CONTACT ALLERGIES IN PATIENTS WITH LEG ULCERS

Dissertation Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In fulfilment of the regulations for the award of the degree

M.D.

DERMATOLOGY, VENEREOLOGY AND LEPROLOGY

DEPARTMENT OF DERMATOLOGY, VENEROLOGY AND LEPROLOGY

PSG INSTITUTE OF MEDICAL SCIENCE AND RESEARCH
THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY
CHENNAI, TAMILNADU

APRIL 2015

CERTIFICATE

This is certify that the thesis entitled **" CONTACT ALLERGIES IN PATIENTS WITH LEG ULCERS"** is a bonafide work of **DR. REVATHI K.** done under the direct guidance and supervision of **DR. REENA RAI, MD,** in the department of Dermatology, Venereology and Leprology, PSG Institute of Medical Sciences and Research, Coimbatore in fulfillment of the regulations of Dr.MGR Medical University for the award of MD degree in Dermatology, Venereology and Leprology.

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I hereby declare that this dissertation entitled **" CONTACT ALLERGIES IN PATIENTS WITH LEG ULCERS"**was prepared by me under the direct guidance and supervision of **DR. REENA RAI, MD,** PSG Institute of Medical Sciences and Research, Coimbatore.

The dissertation is submitted to the Tamilnadu Dr.MGR Medical University in fulfillment of the University regulation for the award of MD degree in Dermatology, Venereology and Leprology. This dissertation has not been submitted for the award of any other Degree or Diploma.

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January 22, 2013

To
Dr K Revathi
Postgraduate
Department of Dermatology
PSG Hospitals
Coimbatore

Ref.: Proposal titled: *'Contact Allergies in patients with leg ulcers'*

Sub.: Ethics Committee Approval for the study

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 31st December, 2012 in its full board review meeting held at College Council Room, PSG IMS&R, between 2.30 pm and 4.30 pm, and discussed your application to conduct the study entitled:

"Contact Allergies in patients with leg ulcers"

The following documents were received for review:

1. Duly filled application form
2. Proposal
3. Informed Consent forms in English and Tamil
4. Patient Information sheet
5. Proforma
6. CV

The members who attended the meeting at which your study proposal was discussed are as follows:

Sl. No.	Name of the Member of IHEC	Qualification	Area of Expertise	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
1	Dr. S. Bhuvaneshwari (Member-Secretary, IHEC)	MD	Clinical Pharmacology	Female	Yes	Yes
2	Mrs. R. Geetha	+2	Lay person	Female	No	Yes
3	Mr Gowpathy Velappan	BA., BL	Legal Advisor	Male	No	Yes
4	Mrs G Malarvizhi	M Sc	Nursing	Female	Yes	No
5	Mr. R. Nandakumar (Vice-Chairperson, IHEC)	BA., BL	Legal Expert	Male	No	Yes
6	Dr. G. Rajendiran	DM	Clinician (Cardiology)	Male	Yes	No
7	Dr. V. Ramamurthy	Ph D	Biotechnology	Male	Yes	Yes
8	Dr. M. Ramanathan	M Pharm, Ph D	Non-Medical (Pharmacy)	Male	Yes	No

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9	Dr. P. Sathyan (Chairperson, IHEC)	DO, DNB	Clinician (Opthalmology)	Male	No	No
10	Dr. Seetha Panicker	MD	Clinician (Obstetrics & Gyanaecology)	Female	Yes	Yes
11	Dr. S. Shanthakumari	MD	Pathology, Ethicist	Female	Yes	Yes
12	Dr. Y.S. Sivan	Ph D	Social Scientist (Sociology)	Male	Yes	Yes
13	Dr. Sudha Ramalingam (Alternate Member-Secretary, IHEC)	MD	Public Health, Epidemiology, Genetics, Ethicist	Female	Yes	Yes
14	Mrs. K. Uma Maheswari	M Sc, M Phil. B Ed	Botany	Female	No	Yes
15	Dr. D. Vijaya	M Sc, Ph D	Basic Medical Sciences (Biochemistry)	Female	Yes	Yes

After due consideration, the committee has decided to approve the above proposal.

The approval is valid for one year.

We request you to intimate the date of initiation of the study to IHEC, PSG IMS&R and also, after completion of the project, please submit completion report to IHEC.

We hereby confirm that neither you nor any of your study team members have participated in the voting/ decision making procedure of the committee. The members of the committee who have participated in the voting/ decision making procedure of the committee do not have any conflict of interest in the referenced study.

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

Non-adherence to the Standard Operating Procedures (SOP) of the Institutional Human Ethics Committee (IHEC) and national and international ethical guidelines shall result in withdrawal of approval (suspension or termination of the study). SOP will be revised from time to time and revisions are applicable prospectively to ongoing studies approved prior to such revisions.

PIs are required to send progress reports (in the form of an extended abstract with publications if any) to the IHEC every six months (and a month before expiry of approval date, if renewal of approval is being sought).

Request for renewal must be made at least a month ahead of the expiry of validity along with a copy of the progress report.

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

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Member - Secretary
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PSG Institute of Medical Sciences & Research
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January 27, 2014

To
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Coimbatore

The Institutional Human Ethics Committee, PSG IMS & R, Coimbatore -4, has reviewed your proposal on 22nd January, 2014 in its expedited review meeting held at IHEC Secretariat, PSG IMS&R, between 10.00 am and 11.00 am, and discussed your application to renew the study entitled:

" *Contact Allergens in patients with leg ulcers*"

The following documents were received for review:

1. Application for renewal
2. Status report of the study

After due consideration, the Committee has decided to renew the approval for the above study.

The members who attended the meeting held on at which your proposal was discussed, are listed below:

Name	Qualification	Responsibility in IHEC	Gender	Affiliation to the Institution Yes/No	Present at the meeting Yes/No
Dr P Sathyan	DO, DNB	Clinician, Chairperson	Male	No	Yes
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Dr Sudha Ramalingam	M.D	Epidemiologist Alt. Member – Secretary	Female	Yes	Yes
Dr D Vijaya	Ph D	Member – Basic Scientist	Female	Yes	Yes

The renewal is valid for one year (From 22.01.2014 to 21.01.2015).

This Ethics Committee is organized and operates according to Good Clinical Practice and Schedule Y requirements.

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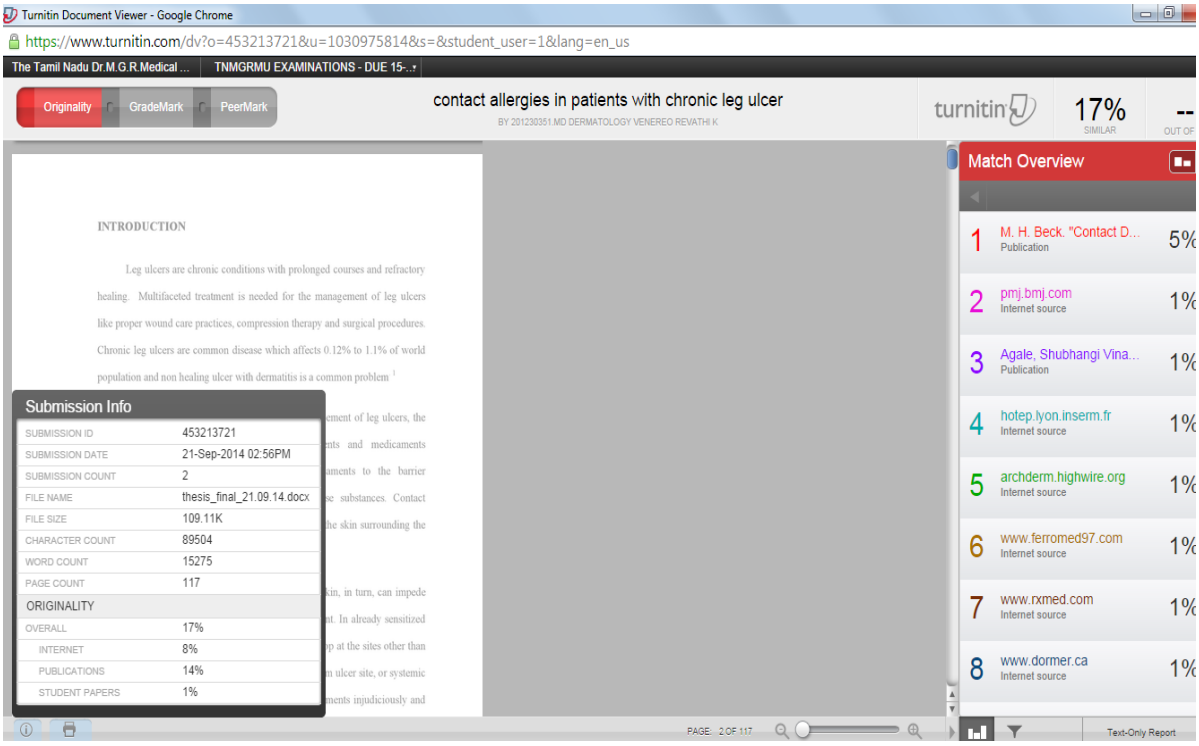
Kindly note this approval is subject to ratification in the forthcoming full board review meeting of the IHEC.

Yours truly,

SECRETARY
PSG IMS&R
COIMBATORE-641004.
INSTITUTIONAL HUMAN ETHICS COMMITTEE

Dr S Bhuvaneshwari
Member – Secretary

Proposal No. 12/127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Leg ulcers are chronic conditions with prolonged courses and refractory healing. Multifaceted treatment is needed for the management of leg ulcers like proper wound care practices, compression therapy and surgical procedures. Chronic leg ulcers are common disease which affects 0.12% to 1.1% of world population and non healing ulcer with dermatitis is a common problem [1]
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INTRODUCTION

INTRODUCTION

Leg ulcers are chronic conditions with prolonged courses and refractory healing. Multifaceted treatment is needed for the management of leg ulcers like proper wound care practices, compression therapy and surgical procedures. Chronic leg ulcers are common disease which affects 0.12% to 1.1% of world population and non healing ulcer with dermatitis is a common problem.[1]

Since the time duration is longer for the management of leg ulcers, the patients are exposed to many topical medicaments and medicaments incorporated dressing. Application of these medicaments to the barrier disrupted skin lead to contact sensitisation to these substances. Contact sensitisation will lead to allergic contact dermatitis of the skin surrounding the leg ulcers.[2]

Allergic contact dermatitis of the surrounding skin, in turn, can impede the healing of ulcers and restrict the choice of treatment. In already sensitized leg ulcer patients, allergic contact dermatitis can develop at the sites other than legs due to direct allergens exposure, dissemination from ulcer site, or systemic spread.[3] In India, patients tend to use topical medicaments injudiciously and frequently because topical medicaments are available over the counter. So chances of contact allergy are more in our country.

The high incidence of contact sensitization in the leg ulcer patient is due to

1. The intrinsic allergenic properties of different ointments, creams and wound care products used to heal the ulcer
2. The excessive duration of use of these medicaments
3. The disrupted skin barrier to which these products are applied.[4] These conditions may lead to contact dermatitis of the leg, ultimately impairing healing and prolonged morbidity associated with leg ulcerations. Recurrence of leg ulcers can be due to persistent or recurrent dermatitis.

The spectrum of the most frequent contact allergens among leg ulcer patients mainly depends on the local practice of wound treatment. One study reported a direct relationship between the duration of leg ulcers and the number of multiple positive allergen sensitivities. From this study findings suggest that an ulcer of long duration has greater opportunity for contact with different allergens and leads to increased sensitivity to this allergens.[5]

Contact sensitisation rates are very high, ranging from 60%-80% in various studies.[2] One study reported at least one positive patch test reaction to the allergens of the European baseline series were documented in 80% of the patients.[6] In a North American study showed that 63% of the patients had one or more allergen sensitizations.[7] In another study among the 423 patients, 73% had positive patch test reaction.[8]

Although several studies have conducted with contact allergy in leg ulcer patients in other countries, studies using leg ulcer series has not been conducted in India. Hence we have conducted study in leg ulcer patients to detect contact sensitisation by using leg ulcer series patch test. Because of higher proportion of contact allergies in chronic leg ulcer patients suggest that all leg ulcers with or without associated dermatitis should be patch tested with leg ulcer series.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1 To determine the frequency of contact sensitization in patients with leg ulcers using a leg ulcer patch test series.

2. Revealing the associations between chronic leg ulcers and contact sensitization.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Leg Ulcers

Leg ulcers are a common condition affecting 0.12% - 1.1% of the population worldwide.[1] It refers to full thickness skin loss on the leg or foot. Among the various causes of leg ulcers, 70% of them are due to venous disorder, 20% of them are due to mixed arterial and venous disease and 10% of leg ulcers are due to other causes Ex.neuropathy, infections, malignancy, and haematological disease.

According to few Indian studies, prevalence of chronic leg ulcer is 4.5 per 1000 population and the incidence of acute ulcer is 10.5 per 1000 population.[9]

Wound healing society estimated that 15% of older adults in the United States suffer from chronic leg ulcer. Almost 2 to 3 million new cases are diagnosed per year in America. The prevalence of vascular ulcer in the United States is 500,000 to 600,000. Annual incidence of leg ulcer in UK is 3.5 per 1000 individuals and annual incidence in Switzerland is 0.2 per 1000 individuals.[10]

One study in Ireland reported that prevalence was 0.12% but prevalence was 1.03% in the patients aged 70 years and over. Women were twice affected than males. Venous disease responsible for 81% of ulcers and the arterial disease accounted for 16.3% of ulcers. Leg ulcers are an important cause of morbidity in ageing population.[11]

Leg ulcers can be classified according to duration of ulcer

1. **Acute leg ulcer** : Ulcer persists less than 6 weeks duration

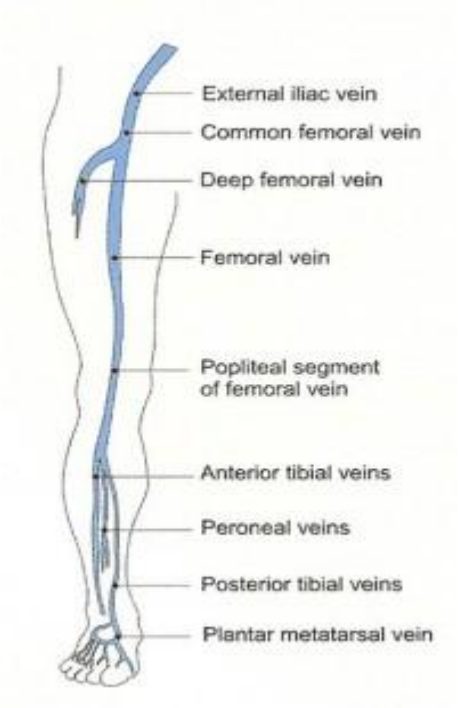
2. **Chronic leg ulcer**: Ulcer persists more than 6 weeks duration.[12]

Table 1: Various causes of leg ulcers .[13]

1. Vascular disease i. Venous disease Ex .venous stasis ulcer ii. Arterial disease Ex.atherosclerosis, hypertensive ulcers, thrombhoangitis obliterans iii. Mixed (both arterial and venous) iv. Lymphedema Ex.congenital lymphedema,post surgical and post infectious lymphedema v. Vasculitis Ex.polyarteritis nodosa, systemic lupus erythematosus. Rhematoid vasculitis	**2.Hematological abnormalities** i.Disorder of red blood cells Ex.Thalassemia, sickle cell anemia, polycythemia vera ii.Disorder of white blood cells Ex .leukemia iii.Dysproteinemia Ex.cryoglobulinemia,macroglobulinemia iv. Hypercoagulable states Ex .Protein C and protein S deficiency,antiphospholipid antibody syndrome paroxysmal nocturnal hemoglobinuria
3. Neuropathic ulcers i. Diabetes mellitus ii.Hansen's disease iii. Tabes dorsalis	**4. Infections** i.Bacterial infection ex.staphylococcus aureus,streptococcus ii.Spirochetal ex. Syphilis iii.Opportunistic infection in immunocompromised iv.Fungal infection ex.deep fungal infection, mycetoma
5.Neoplasms i.Basal cell carcinoma ii. Squamous cell carcinoma	**6. Drugs** i.Ergotism ii.Halogens iii.Hydroxyl urea iv.Anticoagulant necrosis
7. Metabolic disorder i.Diabetes mellitus ii.Gout iii.Porphyria cutanea tarda iv.Prolidase deficiency	**8 .Miscellaneous** i.Pyoderma gangrenosum. ii.Epidermolysis bullosa iii.Ulcerative lichen planus iv.Idiopathic v.Klinefelter's syndrome

Venous Ulcers

Venous ulcers are also called as gravitational ulcer, stasis ulcer, varicose ulcer and hypostatic ulcer. Venous ulcer is a complication of varicose veins and deep vein thrombosis.[14]



Anatomy of lower limb veins:

Lower limb veins can be divided into

1. Superficial veins
2. Deep veins
3. Perforator veins

Fig: Veins of the lower limb

1. **Superficial veins**

Superficial veins are thick-walled and lie in the superficial fascia on the surface of the deep fascia. Superficial veins contain multiple valves which is important to facilitate blood flow towards heart. In the lower limbs venous blood flows from the skin to superficial vein which drain into deep vein.

i. Long or great saphenous vein and its tributaries

ii. Short/small saphenous vein and its tributaries

2. Deep Veins

i. Femoral Veins
ii. Anterior and posterior tibial veins
iii. Popliteal Veins
iv. Peroneal veins
v. Medial and lateral plantar veins
vi. Dorsalis pedis

3. Pumping Veins: These veins are venous sinuses which pump blood towards heart. They are also known as the peripheral heart.[15]

Perforator Veins

Perforator veins connect superficial veins to deep veins at various levels

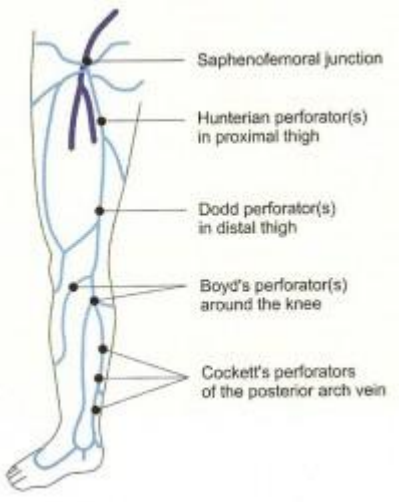


Fig 2: Perforator veins of the lower limb

Types :

1. Hunter's perforator in the thigh

2. Mid thigh perforators (Dodd)

3. Gastronemius Perforators (of boyd)

4. Lower leg perforators (of Cockett)

5. Ankle perforators (May or kuster).[15]

Physiology of venous blood flow

Veins are thin-walled vessels and collapsible. Lower limb veins contain multiple valves and the number of valves decreases proximally.

Factors responsible for venous return

1. Pumping action of vein is increased by aterial pressure across the capillary

2. Calf musculovenous pump: Pressure in the calf muscles increases to 200-300mm Hg during contraction phase of walking. This pressure pumps the blood towards the heart. During relaxation phase, pressure in the calf muscle is decreased. It allows blood to flow from superficial veins to deep veins through perforators. While walking, pressure in the superficial veins at the level of ankle is 20 mmHg.

3. While walking, foot pump mechanism also propels blood from plantar veins into the leg veins.

4. Gravity.[16]

Varicose veins

They are dilated, tortuous elongated veins. The prevalence of varicose veins in the western population is 10-50%.

Primary varicose veins

They have no obvious underlying cause. They are associated with valvular incompetence.

Secondary varicose veins

They are the result of raised endoluminal venous pressure. Post – thrombotic damage is the most common cause for secondary varicose veins.[17]

Risk factors for varicose veins[18]

1. Hereditary

Several studies have reported a genetic predisposition to the development of varicosities. This may be due to abnormalities in the FOXC2 gene

2. Age

3. Sex: High prevalence is seen in women

4. Pregnancy

5. Other factors: obesity, occupations which involve prolonged standing.

Pathogenesis of venous ulcer

Various theories have been postulated to explain the pathomechanism of venous ulceration.

1. Capillary stasis

Homans stated that stasis of venous blood gave rise to the development of anoxia which could lead to venous ulcers.[19]

2. Fibrin cuff-theory

This theory was postulated by Browse and Burnand. Chronic venous in sufficiency is associated with high venous pressure which leads to leakage of large molecules such as fibrinogen. Fibrinogen polymerize to insoluble fibrin in the interstitial space to form a pericapillary fibrin 'cuff'. This cuff can function as an oxygen diffusion barrier.[20]

3. White Cell Trapping

Coleridge Smith et al. formulated white cell trapping theory. According to this theory leukocytes become trapped in the capillaries, obstructing flow which leads to ischemic ulceration. Adhesion molecules, like intercellular adhesion molecule-1 and vascular cell adhesion molecule -1, become over expressed in CVI leading too continuous migration of leucocytes to the dermis.[21]

4. Trapping growth factors

Falanga and Eaglestein postulated that in CVI patients, the pericapillary fibrin cuffs prevent the transfer of growth factors. This may leads to delayed wound healing.[22]

5. Multicausal model: The Maastricht model

Risk factors for venous ulceration[23]

Direct risk factors

1. Varicosities
2. Chronic venous insufficiency
3. Deep vein thrombosis (DVT)
4. Poor function of calf muscle
5. Arterio venous malformation
6. Obesity
7. History of leg bone fracture

Indirect factors

1. All risk factors which lead to deep vein thrombosis Ex.protein C and protein S deficiency.
2. Family history of varicosities.

Venous Leg Ulcer Characteristics[23]

Venous ulcer is located in the gaiter area of the leg, around the medial malleoli. Ulceration can be discrete or circumferential. The ulcer bed is usually covered with a fibrinous layer mixed with granulation tissue. Ulcer edge is irregular and sloping. Pitting pedal edema is seen which is worse towards the end of the day.In chronic venous insufficiency, lipodermatosclerosis can occur. Severe lipodermatosclerosis leads to atrophic blanche and inverted champagne bottle appearance of leg. Extravasation of RBC into the skin leads to pigmentation around ulcer site.

Pathogenesis of venous ulcer[24]

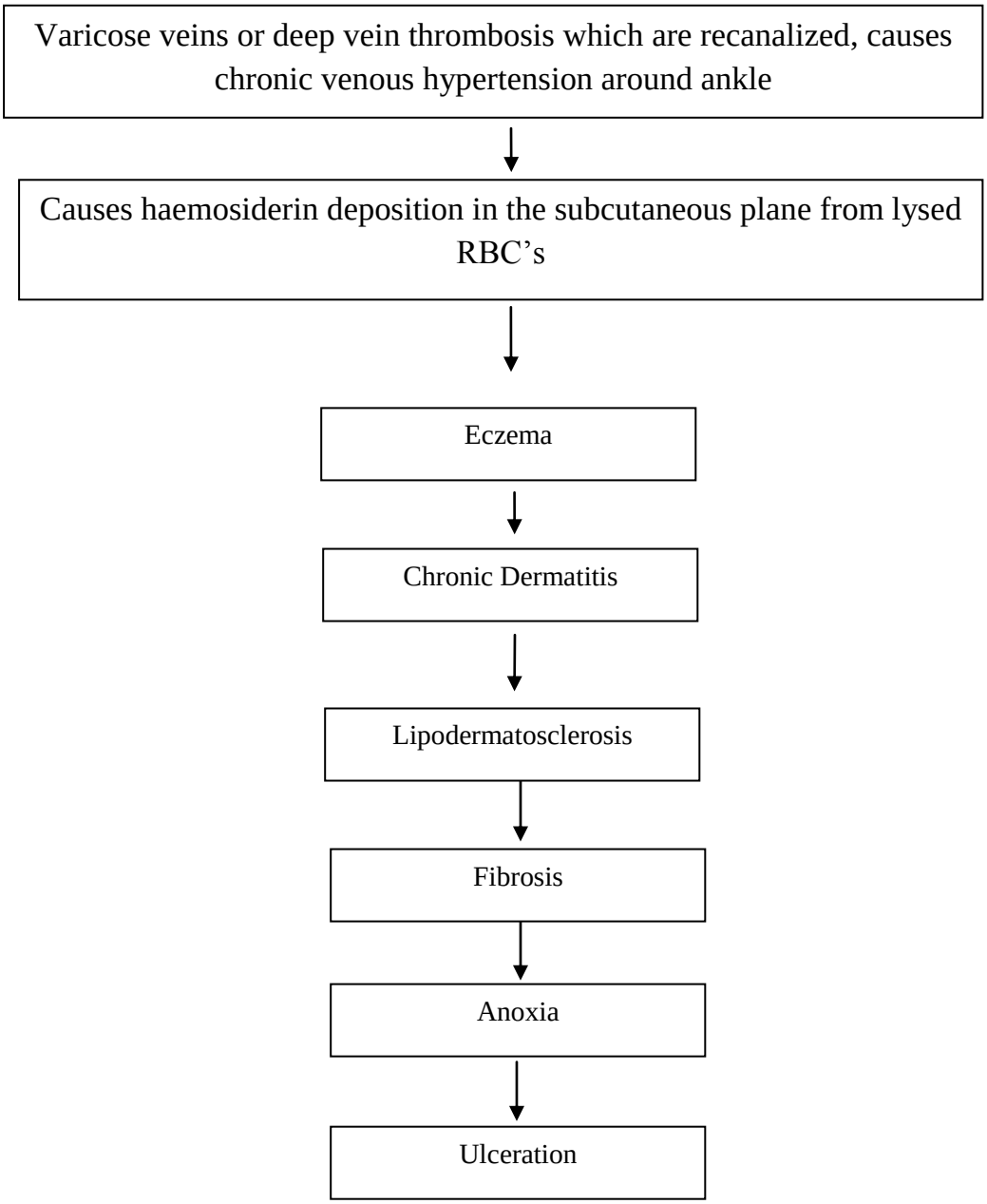


Table - 2

THE DIFFERENCE BETWEEN VENOUS AND ARTERIAL ULCER[25]

	Venous ulcer	Arterial ulcer
History	Previous history of DVT Varicose veins Reduced mobility Obesity Pregnancy	Diabetes Hypertension Smoking Previous history of peripheral vascular disease
Complaints	Throbbing,aching,swelling of limbs and heavy feeling in legs Improves with elevation of limb	Intermittent claudication Rest pain in later stages
Position of ulcer	Gaiter area of the leg Common site is medial malleolar region	Lateral malleolus and tibial area, toes and feet (over pressure points)
Ulcer characteristics	Single or multiple ulcers with irregular borders and sloping edge, shallow ulcers, moderate to heavy exudates	Punched out, occasionally deep, presence of necrotic tissue, low exudates
Condition of lower limb	Limb edema, haemosiderin staining, varicose veins, lipodermatosclerosis, inverted champagne bottle appearance, peripheral pulsation present	Thin shiny ,dry skin with loss of hair, cold limbs, pallor on leg elevation, absence or weak peripheral pulses

Arterial ulcers

Arterial or arteriolar occlusion due to any reason may result in ischemia of the skin which may lead to ulceration. Peripheral vascular disease, diabetes and vasculitis might lead to ischemic limb resulting in ulceration.

Three mechanisms are involved in the pathogenesis of arterial ulcer

1. Extramural 'strangulation' .Ex. scar tissue and radio dermatitis

2. Mural thickening or accretion .Ex.atherosclerosis

3. Intramural restriction of blood flow .Ex. disorders of micro vascular occlusion[27]

Trophic ulcer

The Greek word trophe means "Nutrition".

Trophic ulcer is an "Ulcer due to impaired nutrition of the part".

Classification

1. Neurogenic Ulcer:	Ex.hansens disease, diabetic neuropathy, Syringomyelia, pressure ulcers, alcoholic neuropathy.
2. Vascular	
i.Arterial:	Ex. peripheral vascular disease, atherosclerosis, diabetes.
ii.Venous:	Ex.venous stasis ulcers.
3.Systemic Causes	
Malnutrition:	Ex.vitamin B12 deficiency

Neurogenic Ulcers:

In neuropathy there is loss of pain sensation. Due to repetitive trauma, shearing and frictional forces leads to ulceration.

Etiology and Pathogenesis

Dr. Paul Wilson Brand worked with south Indian leprosy patients in mid 20th century. He explained about the pathogenesis and various complications of leprosy. He said "Pain is God's greatest gift to mankind".[28]

Three reasons for plantar ulceration

1. Injuries from without

Because of loss of sensation, the sole is injured from outside and it is ignored which become infected and leads to a sore.

2. Infection through a fissure in the skin

The dry, anesthetic skin develops fissures or cracks in corns and callosities and become infected, and a sore develops.

3. Breakdown of tissue from with –in (due to walking)

While walking the forepart of the foot is subjected to stress and strain which are countered by foot muscle. Due to paralysis of foot muscle, certain areas are overloaded, causes the tissues to break down, leading to secondary ulceration.

Stages of trophic ulcer

1. Threatened ulceration. 2. Concealed ulceration (stage of 'necrosis blister').
3. Open ulceration[29]

Diabetic foot ulcer

The pathogenesis of diabetic ulcer is multifactorial. It is due to nerve damage and neuropathy, ischemic damage and peripheral vascular disease. The incidence of neuroischaemic leg ulcers is 52.3%, neuropathic leg ulcers 36% and ischemic leg ulcers 11.7%.[30]

Table 3 :Wagner classification for diabetic foot ulcers[30]	
Grade	Description of ulcer
0	Preulcerative lesion/healed lesion
I	superficial ulcers
II	Ulcers deeper to subcutaneous tissue exposing soft tissues or bone
III	Abscess formation underneath/osteomyelitis
IV	Gangrene of part of the tissues/limb
V	Gangrene of the entire one area

Haematological disorders

Non–healing ulcers are a feature of sickle cell disease, hereditary spherocytosis, thalasaemia and other haemolytic anaemia's due to blockage of microcirculation. Thrombotic and occlusive disease can lead to rapid skin necrosis and gangrene. Ex. Protein C and protein S deficiency.[31]

Infections

Infections can lead to ulceration, which is slow to heal because of associated factors. Ex. cellulitis, thromophlebitis. Primary streptococcal ulcer is rare, but streptococcus pyogens or staphylococcus aureus can complicate existing ulcer. Tuberculous cutaneous ulcer may occur in erythema induratum.[32]

Hypertensive ulcer (Martorell's ulcer)

Hypertensive ulcer was first described by Martorell and by Hines. Hypertensive ulcers are superficial ulcers with bilateral distribution. Peripheral pulses are present. The ulcer is preceded by a small macular cyanotic lesion situated on the anterior external aspect of the leg. It is seen in long standing, poorly controlled hypertensive patients. Beta blockers should be avoided.[33]

Rheumatoid Arthritis/Vasculitis

The leg ulcer develops on the shin or ankle after trauma, is related to vasculitis, and difficult to heal. Delayed ulcer healing is due to impaired mobility which contributes to poor muscle pump. The oedema is also difficult to control. Rheumatoid ulcers are due to rheumatoid arteritis. Ulceration of rheumatoid nodules is not common except at pressure points.[34]

Ulceration due to Dermatitis Artefacta

This ulceration may be difficult to diagnose. Clinical suspicion can be raised by the following:

1. Unusual appearance and site
2. After trauma at work place with possible compensation issues
3. Angulate in shape

If any of history recurrence we can do biopsy to show up "out-side-in" damage, that is, disproportionate damage to the epidermis compared with the dermis.[31]

Pyoderma gangrenosum (PG)

Pyoderma gangrenosum is a non -infectious netrophilic dermatoses. It is rare condition and the diagnosis based on the clinical features and exclusion of other causes of ulceration. It can be associated with inflammatory bowel disease, thyroid disease, rheumatoid arthritis and leukemia etc. Histo pathological features of PG are not diagnostic but can be helpful.[28]

Management of Chronic Leg Ulcer.

Ulcer examination

1. Site
2. Size
3. Appearance
4. Base
5. Exudates level
6. Surrounding skin

The surrounding region could be examined for edema, erythema, temperature, indurations, pigmentation, maceration, scars, hair pattern, gangrenous digits, cyanosis, capillary refill and varicose vein.[25]

Leg Examination

1. Palpation of peripheral pulses
2. To search for signs of venous hypertension Ex. Haemosiderin pigmentation, stasis dermatitis, indurations, lipodermatosclerosis and atrophic blanche
3. To assess the range of hip, knee and ankle movements
4. Sensation could be tested to rule out Hansean's disease and peripheral neuropathy.[25]

Laboratory evaluation of leg ulcers

1. Blood Investigations

i. Complete blood count and erythrocyte sedimentation rate: To rule out infection, anemia and polycythemia

ii. Blood sugar level for diabetes

iii. Liver function test

iv. Renal function test

v. Serum transferrin, ferritin, vitamin A, C, zinc, iron – to rule out nutritional deficiency.

vi. Serum homocystiene levels

2. **Laboratory test for Vasculitis**

Urine analysis for proteinuria, hematuria, antinuclear antibodies, rheumatoid factor,complement C4,circulating immune complexes, par proteins, immunoglobulin fractions, antineutrophil cytoplasamic antibodies, serological tests.

3. **Laboratory screening tests for clotting disorders**

Activated partial thromboplastin time, prothrombin time, thrombin time, factor V(leiden) mutation, factor II mutation, antithrombin-III, protein C and protein S,and lupus anticoagulant, anticardiolipin

4. **Wound swabs** for bacterial culture and sensitivity (level C)

5. Tissue sample for mycobacterial and fungal cultures

6. Wedge biopsies including ulcer margin and bed – to rule out malignancy, vasculitis and panniculitis (level D)

7. Venous Doppler (Colour Doppler duplex ultrasound)

8. Arterial Doppler is indicated in patients with ischemic rest pain, claudication, and impending gangrene.

When peripheral pulses are not palpable, Doppler flow meter is used to measure the pulsation over the dorsalis pedis and posterior tibial arteries Ankle brachial pressure index is calculated as follows (level D).

$$\text{ABPI} = \frac{\text{Systolic pressure in the ankle}}{\text{Higher of the two systolic pressure obtained from Brachial arteries in both arms}}$$

9. Plain radiography of foot along with CT and MRI – To rule out osteomyelitis and malignancy

10. Patch testing (level C): To rule out allergic contact dermatitis to medicaments and preservatives (when patient has been applying topical preparation for a long time.)

Treatment

Venous ulcers

First we have to exclude arterial disease. Primary aim of treatment is to reduce venous hypertension, promote wound healing and prevent recurrences. Venous hypertension may be reduced by simple leg elevation and compression therapy.

Compression Therapy

The aim of compression therapy is to maintain sustained compression of 30-40 mm HG at the ankle level thereby reducing the edema and improving calf muscle pump function and promoting ulcer healing. Multi-layered compression systems are more effective than single-layered compression systems. High compression therapy is more effective than low compression. Graduated multilayer high compression bandage regimens are the first line of treatment for venous ulcer without any complication with ABPI above 0.8[35]

Types of compression devices

1. **Graduated Elastic Compression stocking** (level A)

   According to European standardization commission compression stockings are classified into four categories

   Class I, 15-21 mm HG: For thrombosis prophylaxis

   Class II, 23-32 mm HG: Indicated in mild/moderate oedema, mild chronic venous insufficiency, after sclerotherapy, pregnancy.

   Class III, 34-46 mm HG: Indicated in severe chronic venous insufficiency, severe oedema, lymphedema, post-thrombotic syndrome

   Class IV, >46 mm HG: severe lymphoedema[36]

2. Unna's Boot

Unna's boot contain zinc oxide 5 parts, gelatin 5 parts, boric acid 1 part, glycerin 8 parts and water 6 parts and ichthyol 1 or 2 parts. Moist gauze impregnated with this paste and it is wrapped from behind the first metatarsal up to an inch below the knee. It is applied in a figure-of-8 pattern or adding pleats while wrapping. It may be left in place for 7 days before changing.[35]

3. Four layered bandaging

It is a high compression bandage system that incorporates elastic layers to achieve sustained compression.

Layer 1: Orthopaedic wool

Layer 2: Cotton crepe bandage

Layer 3: Light weight class 3A elastic compression bandage

Layer 4: Class 3B cohesive compression bandage and it retains the bandage in position.

Class 3A: Maintain pressure up to 20 mm HG at the ankle level

Class 3B: Maintains pressure up to 30 mm HG at the ankle level[36]

4. Intermittent Pneumatic Compression

It is mechanical method of delivering compression to swollen limbs. It will increase the venous return, increase the endogenous fibrinolysis, reduce the intravascular coagulation and improve the arterial perfusion. Relieves edema and promotes healing in venous ulcer patients. It is also used to treat lymph edema.[37]

Wound care

Following modalities are practiced in wound care

1. Dressing (level A)
2. Debridement
3. Topical treatment
4. Systemic treatment
5. Biophysical treatment

1. Dressing

Dressing will maintain a moist environment which accelerates wound healing. Frequent application of saline dressings over the wound will helps to keep the wound surface moist, debrides the wound and removes the surface bacteria.

Active dressing deliver substances, such as growth factors which help for wound healing. Interactive dressings are occlusive dressing which provides a favourable microenvironment for the growth of new tissues. Occlusive dressings will control the exudates, infection and eschar is liquefied by autolytic debridement.

Various type of dressing

1. Films

They are thin transparent adhesives. They are made of polyurethane and should be changed every 12-24 hrs. Ex.Tegaderm. This kind of dressing protects the wound from contamination but can strip away the newly forming granulation tissue and used in wounds with moderate exudates.

2. Hydrogels

They are gel like sheets and semitransparent. They are nonadhesive and should be changed every 1-3 days. Ex.Restore hydrogel.

3. Hydrocolloid

Dressing contains hydrocolloid with a polyurethane outer coating. Dressing should be changed once a week. Ex.duoderm

4. Collagen

It is available in particle and sheet form. It is obtained from human, porcine and bovine sources. It forms a biodegradable gel over the wound surface Ex.Promogran. This dressing will promotes wound healing by laying down a matrix which leads to new tissue formation and also depletion of free radicals and proteases

5. Alginates

These dressings are biodegradable. They are derived from seaweeds. Alginates dressings can be left in place until soaked with exudates. Ex.sorbsan. They are highly absorbent and haemostatic and dry out the exudating wound making it more painful.[38]

The skin surrounding the ulcer region may be damaged due to excess moisture, proteases and adhesives present in the dressings. So we can use barrier creams and ointments to protect the skin around the ulcer.

Examples

1.Vaseline petroleum jelly

2.Unna's paste[38]

Debridement

Debridement will remove the necrotic debris and promotes the formation of healthy granulation tissue. Various methods of debridement include:

1.Surgical debridement
2.Autolytic debridement
3.Enzymatic debridement
4.Biodebridement

Surgical debridement

By using a curette and scissors chronic wound is converted into acute wound which leads to neutrophils and macrophages recruitment. These cells secrete growth factors and phagocytise the bacteria and nonviable tissue.[38]

Bio debridement

Larvae of luciliasericata ("green bottle" blow fly) will selectively debrides the dead tissue and tissue debris by secreting collagenase.[39]

Enzymatic debridement

Application of topical protease preparation will target the fibrin and collagen of necrotic tissue. Ex.papain urea preparation obtained from papaya and collagenase derived from clostridium histolyticum.[40]

Autolytic debridement

By giving occlusive dressing, gentle separation of slough from wound bed will occur slowly in a moist wound environment. Proteases within the

wound space will liquefy the necrotic tissue and it is useful in patients with bleeding tendencies[38, 40]

Topical treatment

Secondary bacterial infections will interfere with wound healing. So we can use topical antiseptic and antibiotics have been used to reduce the infection.

Examples of various topical preparations are

1.Silver compounds: it is effective against gram negative bacterias

2.Twenty percent benzoyl peroxide

3.Iodosorb

4.Metronidazole gel - anaerobic coverage

5.Retapamulin,mupirocin ointment

6.Modifieddakin solution

7.Neomycin and bacitracin should be avoided because of their contact sensitivity.

8.Honey dressings are not recommended routinely.[41]

SYSTEMIC THERAPY

1.Antibiotics

In chronic leg ulcer patients, systemic antibiotics should not be used, unless there is clinical evidence of infection(level C)

2.**Pentoxifylline** is used to increase microcirculatory flow but exact mechanism is not known(level A)

3.**Stanozolol**: It is an anabolic steroid reduces the pain and dermal thickness in acute lipodermatosclerosis

4.Aspirin

5.Micronized purified flavonoid fraction

6.Mesoglycan

7.Zinc[41]

SKIN GRAFTING

1. Pinch Grafts

Pinch grafts are useful for small nonhealing ulcers with clean ulcer bed and healthy granulation tissue. It is a simple technique but cobble stoning of the ulcer site can occur.[42]

2. Split Thickness Skin Grafting: epidermis and portion of the dermis from the donor site is transferred to ulcer site. This graft covers large defects.

3.**Cultured Epidermal Grafts**

Cultured epidermal cells(keratinocytes) can be derived from patients own skin(auto graft) or from donor(allograft)

4. Dermal Substitutes

It is derived from human newborn foreskin fibroblast cells which are seeded on to a bio absorbable mesh.

5. Composite Grafts(Apligraf)

It contains both dermal and epidermal components. It is a living bilayered skin substitute which is manufactured from neonatal foreskin keratinocytes and fibroblasts with bovine type I collagen.[43]

Other therapies

Biophysical modalities of treatment

1. Electromagnetic therapy

2. Low frequency ultrasound (34KHz) – temporary stimulation of microcirculation

3. Negative pressure devices/vacuum assisted closure - sub atmospheric pressure of 100-125 mm HG is applied in a continuous or intermittent manner.

4 .Hyperbaric oxygen therapy[44]

LASER FOR LEG VEINS

1.Pulsed dye laser(PDL)

For leg veins less than 0.2mm in diameter ,PDL laser 585nm and pulse duration 1-40ms is used.

2. Diode Laser (800nm)

Long pulsed Nd:YAG laser(1064mm),long pulsed alexandrite laser(755nm), intense pulsed light(515-1200nm) can be used for treating leg telangiectasias.[45]

Sclerotherapy

Introduction of a chemical (Ex. hypertonic saline, sodium tetradecyl sulphate, polidocanol) into the vein will induce endothelial damage which leads to thrombosis, subsequent fibrosis and occlusion.

Endovenous techniques for varicose vein

1. Radiofrequency ablation

2. Endovenous laser ablation[46]

Surgical methods for varicose veins

1. Saphenofemoral ligation
2. Great saphenous vein stripping
3. Sub facial ligation of perforators
4. Phlebectomies
5. Subfascial endoscopic perforator surgery.

TREATMENT OF ARTERIAL ULCER

1. The patient should stop smoking and diabetes or hypertension must be well controlled. Lipid lowering drugs like statins, antiplatelet drugs like aspirin,clopidogrel and cilostazol (phosphodiesterase III inhibitor) will prevent ischemic events.
2. Regular graded exercise must be encouraged to promote development of collateral circulation. Pressure area must be protected.
3. The head of the patient's bed should be raised by 4-6 inches to encourage gravity dependent arterial flow and limbs should be kept warm.
4. If rest pain or acute infection is present patient must be referred to vascular surgeon. endarterectomy, balloon angioplasty ,femoral bypass graft may necessary in selected cases.[23]

Management of diabetic ulcer and neuropathic ulcers.

The patient should follow this instructions

1. Patient should stop smoking

2. Regular inspection of the legs/feet for scratch mark,blisters,etc

3.Wash the feet with Luke warm water daily and careful drying between the toes

4. Use emollients

5. Regular inspection of shoes and wear properly fitting shoes

6. Avoidance of sandals and pointed shoes

7. Do not walk bare foot

8. Avoid walking long distance

9. Report to doctor even for slightest foot complaints

Aggressive debridement of the dead tissue and the surrounding callus should be done. Occlusive dressing like alginates will absorb the exudates and maintain the moist environment. For ulcers will requires rest with foot elevation and if infection is severe, antibiotics can be given. Foot X-ray can be taken to rule out osteomyelitis of bone. Osteomyelitis is commonest cause for nonhealing ulcer. Surgical intervention like wound debridement and removal of osteomyelitic bone will be done in this kind of ulcer. Once infection is controlled, adequate rest and offloading of the foot can achieve ulcer healing.[23]

History of patch testing

During 17^{th}, 18^{th}, 19^{th} centuries some researchers reproduced contact dermatitis by applying responsible agent to intact skin. In 1847 Staedeler first described blotting paper strip method to demonstrate idiosyncrasy. In 1895 Jadassohn described the role of patch testing in dermatitis medicamentosa and he is known as father of patch testing.[47] Further establishment of patch testing

was contributed by Bloch, Bonnevie and Sulzberger. Standardization of patch testing has been contributed by Sulzberger.[48]

Eczema

Eczema, a term derived from the Greek meaning 'to boil'. It is a clinical and histological pattern of inflammation of the skin. It is seen in a variety of dermatoses with widely diverse aetiologies.

Signs of Eczema:

Dryness, erythema, excoriation, exudation, fissuring, hyperkeratosis, lichenification, papulation and vesiculation.

Histological features of eczema

Spongiosis, varying degree of acanthosis, hyperkeratosis, accompanied by lymphohistiocytic infiltrate in the dermis.[49]

Classification of eczema

Eczema is broadly classified as exogenous and endogenous. External factors play a major role in exogenous eczemas. The term endogenous eczema implies that the eczematous condition is not due to exogenous factors, but is mediated by processes originating within the body. Eczema can also be classified clinicopathologically as acute, sub acute and chronic.[50]

Table - 4

CLASSIFICATION OF ECZEMA[50]

Exogenous eczema	Endogenous eczema
1.Irritant eczema 2.Allergic contact eczema 3.Photoallergic contact eczema 4.Infective eczema 5.Eczematous polymorphic light eruption 6.Dermatophytide 7.Post-trauamtic eczema	1.Atopic eczema 2.Seborrheic eczema 3.Asteatotic eczema 4.Hand eczema 5.Venous eczema 6.Eye lid eczema 7.Discoid eczema etc

Allergic Contact Dermatitis

It is a delayed hypersensitivity reaction which is caused by systemic exposure or ingestion of a contact allergen. It occurs in previously sensitized persons.

History of patch testing

Von Pirquet coined the term 'allergie' in early 20th century from the greek word allos and ergon.[51] Contact allergy was first demonstrated by Bloch and Steiner.[52]

Pathogenesis of Allergic Contact Dermatitis

Jadassohn[53] who described contact allergy in 1895, can be considered as the "father" of contact dermatitis. It is a type IV hypersensitivity reaction. Contact allergens are small-molecule substances of less than 500 daltons[54], so they penetrate the skin barrier

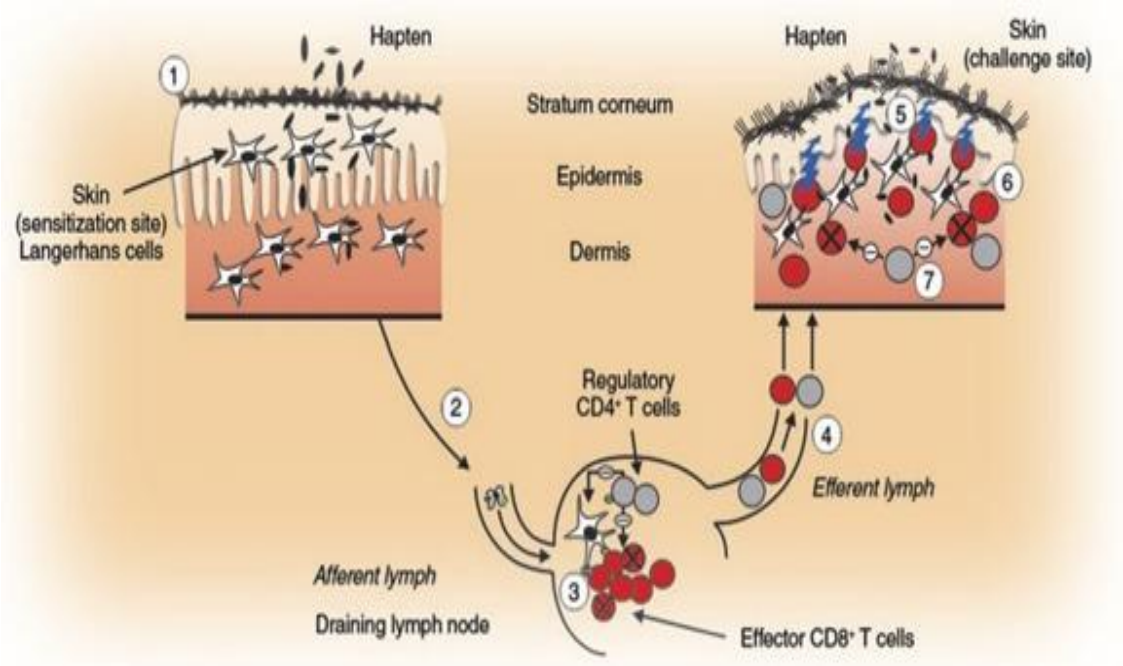


Fig 3 Pathogenesis of Allergic Contact Dermatitis

Path physiology

Step 1 : Haptens penetrate the stratum corneum and binding of haptens to dendritic cells

Step 2 : Hapten-carrying langerhans cells traverse through efferent lymphatic's to lymph node.

Step 3 : Migrating langerhans cells are located in the Para-cortical area of the draining LN where they can present haptenated peptides on MHC class I and II molecules to CD8+and CD4+ T cells, respectively .

Step 4 : Proliferated T cells reach the blood flow through efferent lymphatics

Step 5 : During this process they acquire skin-specific homing antigens (CLA and CCR4)and become memory T cells. Primed T cells preferentially diffuse in the skin after transendothelial migration. At the end of the sensitization step everything is ready for the development of a CS reaction upon challenge with the relevant haptens. Elicitation phase: When the hapten is painted for a second (and subsequent) time, it diffuses through the epidermis and could be loaded by LC or other skin cells expressing MHC molecules, such as keratinocytes and dermal dendritic cells, which are then able to activate trafficking specific T cells

Step 6 : CD8+ cytotoxicT cell activation initiates the inflammatory process through keratinocytes apoptosis and cytokine/chemokine production.(5)

Patch Testing

The 'patch test' is the only practical test for demonstrating contact allergy at present.[56] It is required to identify the cause of allergic contact dermatitis. Some workers find patch testing to be of little value, while others believe that it is generally required to identify the cause of allergic contact dermatitis. Patient selection, expertise in patch testing and criteria for relevance are among the factors accounting for their discrepancy.

Properly applied and correctly interpreted patch test are, at present, the only 'scientific proof' of allergic contact dermatitis. Patch test is a biological test to detect the presence of delayed type of hypersensitivity to specific contact allergens. The patch test is a unique direct "in vivo" test independent of any laboratory procedure.[57.58]

Predisposing factors for Allergic contact dermatitis

Individual

1. Constitution

Sensitization depends upon the individual susceptibility.[59]Certain individuals are more sensitive to a particular substance. The role of atopy in allergic contact dermatitis is a matter of debate. One study reported high prevalence of contact allergy in atopic individual but another study showed same prevalence and others reported decrease in the prevalence of contact allergy.[60]

2.Sex

In one study, women were more susceptible whereas, in another study, men were more susceptible. The reason for the female preponderance is mainly explained by exposure.[61]

3.Race

Afro-Caribbean's are less susceptible compare with white people because of less exposure.[62]

4.Hormones

Amelioration or deterioration of contact dermatitis can occur during pregnancy.. Premenstrual exacerbation of contact allergy has been reported.[63]

5. Age

Positive patch test reactions tend to increase with age, due to exposure various allergens over a life time. Adults are more likely to have occupational or cosmetic allergies whereas old people are more liable to medicament.[64]

6.Contact dermatitis in children

Now a day's frequency of childhood allergic contact dermatitis has increased. The commonest allergens are nickel, fragrance, thiomerosal, medicaments, rubber chemicals and resins in footwear.[65]

7.Coincidental Diseases

Patients with debilitating disease such as cancer, hodgekin's lymphoma and mycosis fungoides have impaired capacity for contact sensitization.[66]

8.Medication

Medication can influence patch test reaction. Prednisolone (>15mg/day) and potent topical steroids suppress patch test reactions. Immunomodulators such as ciclosporin and azathioprine may reduce the intensity of patch test reactions.[67] Therapeutic UVB or psoralen UVA therapy can also reduce allergic reactions.

9.Local factors.

Pre –existing or concomitant allergic or irritant dermatitis damages the skin, affecting its barrier function and producing increased opportunities for allergen absorption which leads to secondary sensitization.

Occlusion promotes percutaneous absorption and contributes to the high incidence of medicament dermatitis in stasis dermatitis, leg ulcers, otitis externa and peri anal dermatitis. Acquired sensitivity is more common if an allergens is applied to damaged skin.[68]

Factors that can enhance the risk of sensitization:

1. Increased allergen absorption due to barrier disrupted skin.
2. Recruitment of immune competent cells and cytokines which leads to priming of immunological response
3. Accumulation of mononuclear cells.

Matzinger's 'danger model' concept for sensitization[69]

Contact allergy may develop in the presence of cytokine release from the keratinocytes which is provoked by a coexisting irritant or trauma. If there is no irritancy then tolerance will develop.

Environmental

Certain important environmental factors are

1.Climate

2.Flora and fauna

3.Socio-economic and cultural

1.Climate

UV exposure, heat and relative humidity ,may influence the liability to contact allergy.UVB exposure will diminish the skin's immune response to contact allergens, however reduction in immune responsiveness by UVA exposure is transient due to adaptive mechanism.[70]

Chapping of the skin during winter season predisposes to irritant dermatitis and increases the incidence of false-positive reactions to certain substances such as formaldehyde and propylene glycol.[71] Occlusion and excessive sweating can increase contact allergy from shoes and clothing.

2. Socio-economic and cultural

Exposure to cheap metals, various cosmetics and perfumes may vary according to social class. In the Middle and Far East, the traditional herbal medicines and balms are commonly used to treat skin disorders. In addition ingestion of herbal folk remedies can also cause systemic allergic contact dermatitis. Hair dyes, kumkum and bindi are commonly used by Indian

women.[72] But various cosmetics and sunscreens are mainly used by Western people.

3. Flora and fauna

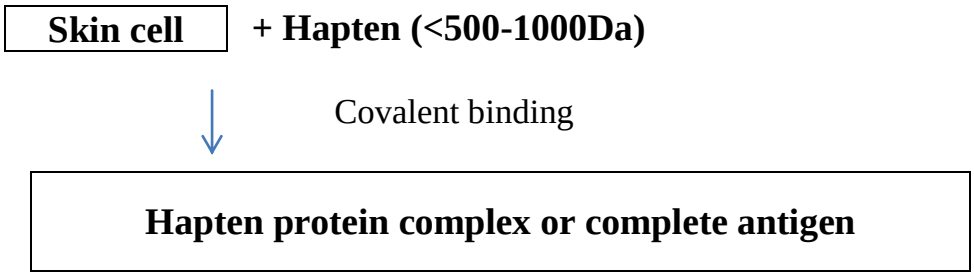
Seasonal variations are most common in plant dermatitis. Many allergic plants especially compositae family plants are destroyed by cold and frosty weather but return during spring and summer season. Geographical location is an important influence. In India parthenium contact dermatitis is more common.

Fauna has only mild influence. European fishermen are liable to contact allergy of exposed skin only during the summer season due to handling of nets which contain bryozoans (marine organism). This is known as 'Dogger Bank Itch' in the United Kingdom. The identified allergen is (2-hydroxyethyl) dimethyl sulfoxonium ion.[73]

Chemical

Skin cell molecules: Contain nucleophilic atoms

Haptenmolecules : Contain electrophilic atoms (positively charged, electron deficit)



Haptens are grouped according to their chemical reactivity or according to functional groups. Some haptens are not allergenic .but they are converted into allergenic molecule by the skin detoxification process (hydroxylation, monoamineoxidases, peroxidases)[74]

Table - 5

CLASSIFICATION OF HAPTENS BASED ON FUNCTIONAL GROUPING[75]

1.Acids	7.amines
2.aldehydes	8.esters
3.diazo compounds	9.epoxides
4.metals	10.halogenated compound
5.ethers	11.quinones
6.unsaturated compound	

Sensitization Potential

It is the capacity of a given allergen to induce sensitization in a group of humans or animals.

Various test procedures to assess the sensitization

1. Maximization test(described by Kligman and Epstein)
3. Open epicutaneous test
4. The Draize test
5. Freud's complete adjuvant test
6. The local lymph node assay
7. The mouse ear swelling test.[76]

Patch Test

Methods

The basis of patch testing is to elicit a delayed type of hypersensitivity response by challenging already sensitized person to particular amount and concentration of allergen and assessing the degree of response. Champers or discs are used for patch testing. Non-occlusive, non-allergenic and non-irritant fixing tape should be used. If the fixing tapes peel off, the patch test should be repeated.

In patients with active eczema we should not carried out patch testing. The patch testing could be delayed until the test site has been clear (at least two weeks). Corticosteroids and other immunosuppressive drugs like methotrexate and azathioprine should be stopped before patch testing. It may reduce the positive patch test reaction. But prednisolone less than 15 mg will not reduce the positive patch test reaction.[77]

Patch testing could be delayed for 28 days following sun bathing. The patches should not be exposed to UV light including sun light. Infants, young children may be patch tested when indicated, but number of allergens tested can be reduced.[78]Pregnant patients should not be patch tested because of adverse effects.

Principles of Patch Testing

1. We should use only known substances in "standard concentration". For unknown substances we can do open or "use" tests with controls
2. In acute dermatitis we should not test
3. Inform the patient to leave the patches on for 48 hours
4. Inform the patient not to shower, get the back wet, or engage in sports. Heavy work should be avoided.
5. Initial reading should be taken at 48 hours and further reading should be taken between 72 and 120 hours.
6. It is difficult to distinguish irritant reaction from allergic reaction. Itching is more common in allergic reaction[79]

Open use test or provocative use test

This test is mainly used for non-irritating substances such as cosmetics. The suspected substance is rubbed onto normal skin in the antecubital fossa. It should be applied twice daily for 1 week, over an area approximately 3 cm in diameter. If no reaction occurs, the test can be considered negative. False negative reactions are common in this method. This test can be used to detect contact urticaria.[79]

Instructions to the patient

1. Patch should be left in place for two days and two nights

2. Patient should not take bath or wash or wet the back during this period

3. Patient should be instructed to avoid tight underclothes

4.To avoid exercise or any heavy physical activity which causes excessive sweating

5.To avoid friction or rubbing and lying on the back because patches will become loose

6.To avoid scratching the patch test site. Report immediately if there is severe itching or irritation

7.To avoid exposure to sunlight/UV light

8.To come after 48 hours and 72/96 hours for patch test reading.

Patch Test Vehicles

Certain allergens may be applied to the skin as they are. To avoid an irritant effect, they should be mixed or dissolved in a vehicle. The test substances should be soluble in the vehicle.

Petrolatum is most commonly used vehicle. Other vehicles are water, alcohol acetone, methylethylketone and olive oil. Irritants such as chloroform and benzene must be avoided. Petrolatum may not be ideal in hot climates. Petrolatum allergic reactions are rare.[80]

Test Material

Patch Testing Materials-Manufacturers

Hermal, D-21462 Reinbeck Germany and chemo technique Diagnostics AB, Modemgatan 9,S-235 39 Vellinge, Sweden or from local distributors.

Finn champers on Scanpor tape is commonly used to apply patch test allergens. They are available in strips of five and ten which consist of small, occlusive aluminium discs. Champers is mounted on non- occlusive tape.

Other systems

1.Square plastic champers(Van Der Bend champers)

2.Oval plastic champers(Epicheck)

3.AL test system: made of aluminium foil covered with polythene.Allergens are adsorbed onto a centrally placed filter paper disc of 10 mm diameter.[81]

TRUE Test

Thin layer rapid use epicutaneous test. Allergens are available ready to use form coated onto polyester patches in a hydrophilic vehicle. It contains only 24 allergens of standard series. It was introduced by Torkil Fischer and Pharmacia. It is a convenient and portable method.[82]

Patch Test Concentration

Suitable concentration is used for patch testing. Excessive concentration will result in false-positive reactions due tom their irritant effect whereas low concentration will produce false-negative results. We should not apply any unknown chemicals or substances.

The precise nature of the material should be decided by questioning the patient and examining the product label. If a positive reaction to an unknown substance occurs, it should not consider as allergic reaction. For unknown substance we can use open use test.[81]

Test dose

1. Finn champers: 20 mg of allergen (petrolatum vehicle) [83]
2. Disposable syringes (container): 5 mm length of test substance (petrolatum).
3. Filter paper champers: 15 micro Ls (fluid vehicle)
4. TRUE test: patches are pre-prepared

Patch Test Site

Back is the preferred site to apply patch test. Allergic and irritant reactions are easily provoked on the upper back. Less suitable sites for patch testing are lateral aspect of arm, fore arm, abdomen and thighs.

Table - 6

Reactivity of various test sites[84]

Test site	Irritant reactions (%)	Allergic reactions (%)
Upper back	100	100
Upper arm	52	72
Lower back	50	95
Fore arm	38	74
Thigh	36	50

Allergens Storage

Allergens should be stored in the dark in a refrigerator at 4 degree C. Certain allergens are unstable if exposed to light. Commercial preparations are labelled with expiry date. If they are not refrigerated properly, homogeneity of allergens may be lost. Rubber pipette caps contaminate the solutions and can cause false-positive patch test reaction in persons sensitive to rubber.

Exposure Time

The mere touch of some allergens can provoke a bullous response in a sensitive person, but some substances even 120 hours of occlusive patch tests can lead to false-negative results. For a well -established allergens, generally 48 hours application time is needed. Reading will be taken 1 hour after removal of patch. Second reading will be taken after 48hous. Some authors have suggested that a Day 5 second reading is better. A single 48hours reading is not advised. If only one test reading is possible, a 96 hours reading has been recommended. Neomycin and corticosteroids are liable to give late reactions.[85]

Marking

Patch test sites are marked with indelible ink or stratum corneum stains. For dark skin we can use fluorescent marking. Marking materials are obtained from allergen suppliers.

Patch Test Reading and Interpretation

Recording of patch test reading is done according to the International Contact Dermatitis Research Group criteria[86]

Drawbacks of ICDRG System

It confuses morphology with interpretation.

Relevance of patch tests[87]

Certain allergen has been demonstrated reliably by careful patch testing does not prove that such allergen was responsible for the dermatitis. The negative patch test does not prove the absence of allergy. Relevance may be considered possible, probable, or certain.

Following questions may be helpful for determining relevance

1. Relevance to the Present Dermatitis

i. Primary cause

ii.Aggravating factor

2. Relevance to a Preceding Bout of Dermatitis

i. Primary cause

ii.Aggravating factor

3. Not Relevant

The strength of patch test reaction depends upon the following factors[88]

1. Barrier function

2. The presence or absence of sweating

3. The atmospheric humidity

4. Test material

5. Technique

6. The reactivity of the individual.

Irritant Patch Test Reaction[87]

Causes for irritant patch test reactions

1. Hyperirritability of the skin

2. Application of an irritating concentration of a test substance

Spill over

One positive test has influenced another test to appear positive.

Certain rules must be followed to avoid irritant reactions[87]

1. Patch testing should be carried out only on the normal skin

2. Irritating concentration of test materials should be avoided\

3. Cleansing the skin with soaps or solvents should be avoided

4. Avoid patch testing with nonstandard substances other than standard series

Janus reaction [87]

It is a non papulo vesicular patch test reaction consisting of palpable erythema and oedema. The significance of these reactions may be determined over time, based on patient's outcome. This mild reaction may or may not be relevant, so further correlation is needed to establish contact allergy.

Irritant reactions are liable to induce stronger reactions at 48 hours than at 96 hours. This is called crescendo-decrescendo effect.

Non- invasive measurement techniques[89]

1 .Laser Doppler flowmetry

2. Replica techniques

3. High-frequency ultrasound

4. Skin reflectance

5. Transepidermal water loss

6. Thermography

Causes of false positive patch test reactions[88]

1. Excessive concentration of allergens

2. Impure patch test substance

3. Excessive amount of allergen applied

4. Vehicles may be irritants

5. Hard material can cause pressure effect

6. Uneven dispersion of allergen

7. Active or recent dermatitis at patch-test site

8. Active dermatitis at distant site

9. Artefact

10 .Irritant reaction due to adhesive tapes

11. Angry back reaction

In case of any doubt, we can repeat the patch test some weeks later. Usage test or ROAT test is used to differentiate allergic reaction from irritant reaction.

Causes of false negative patch-test reactions[88]

1. Insufficient concentration of allergens

The threshold or reactivity has narrow margin so, the concentration of allergen is critical and should be standard.

2. Improper adhesion of patches

3. Patches are applied at wrong site

4. Inadequate amount of allergens applied

5. Pre treatment of test site with topical corticosteroids

6. Inappropriate vehicles may be used

For example, testing with nickel in petrolatum produce negative reaction, whereas testing with nickel in an aqueous solution produce positive reaction

7. Substance may degraded

8. Too early reading

When patch tests are read at Day 2,some positive reactions are missed. Ex.Neomycin and corticosteroids

9. Systemic treatment with immunosuppressant's such as cyclosporine, azathioprine

10. UV irradiation of test site

Sometimes a patch test fails to produce a positive reaction in a sensitized person. The most common cause of false-negative reactions is poor penetration through the skin. Neomycin and corticosteroids will take long period of latency. So late reading should be preferred for this substance. false negative reactions are common with textile allergens, cosmetics, cutting oils, washing materials, medicaments, leather and rubber. Sukanto and associates reported that the topical application of corticosteroids has a suppressive effect on both the intensity and the size of reaction.[90]

Dermatologist hesitate to use patch testing because of following four reasons

1. The amount of time required of the dermatologist
2. The number of visits required of the patient
3. Suitable test materials are not available
4. The risk of patch test complications[87]

Complication of patch testing

1. Active sensitization

A patch test reaction appearing seven or more days after application of patch may denote either delayed expression of a pre-existing sensitivity or sensitization from the patch testing. Active sensitization presents as a strong positive test occurring at around 3 weeks.

The most common cause of sensitization is the use high concentration of the test substance. So patch testing with standard allergens may not produce sensitization. Sometimes persistence of test reactions can continue for several

weeks. Ex.gold sodium thiosulphate. Sensitization is common when patch testing with unrefined wood or plant or patients own material.[91]

Cronin clearly states “active sensitization is a complication of patch test but it is not a hazard. It should not be used as an excuse by the indolent for eschewing this investigation. To reject patch testing is the greater disservice to the patient” [92]

2. Edge Effect

The reaction is more at the periphery of the patch test but at the centre there is little or no reaction. This called as edge effect. Edge effect is due to increased concentration of liquid which act as an irritant. The edge effect will disappear following removal of the patch. However the edge effect which is produced by corticosteroids is different. This edge effect is a sign of allergy and denotes interaction between pharmacological and immunological activity of corticosteroids. Lower concentration of corticosteroid gives positive patch test.[93]

3. Irritant patch test reactions

Irritation may be avoided by using standard procedures. Substances should be investigated toxicologically and allergologically.

4. “Ectopic” Flare of Dermatitis

5. Persistence of a Positive Patch Test Reaction

Contact dermatitis to gold is known to persist for more than a month. To control this reaction we can use intralesional corticosteroids.[93]

6. Koebner Phenomenon

A positive test reaction in a patient who is having psoriasis or lichen planus may reproduce these dermatoses at the test site. This is known as Koebner Phenomenon.

7. Alteration in Pigmentation

Hyperpigmentation from patch tests may occur in darkly pigmented persons. Topical corticosteroids are used to treat this hyperpigmentation. Hydroquinone should be avoided. Severe positive reactions can cause hyperpigmentation or total depigmentation. Irritant reactions may cause hyperpigmentation.[93]

8. Anaphylaxis

Anaphylactic reactions from patch tests are rare manifestation. Anaphylactoid reaction can occur within 30 minutes after application of topical antibiotics such as penicillin, gentamycin, neomycin and bacitracin. Nitrogen mustard can also cause anaphylaxis.

9. Pustular Patch Test Reactions

This reaction can occur from application of nickel and copper sulphates, arsenic trioxide, and mercuric chloride.[93]

10.Bacterial and viral infections

This is very rare side effect. This can occur in patients who are patch tested with fresh plants. In mayo clinic one case was reported. A patient who, after being tested snapdragon plant, developed a necrotizing cellulitis at the test site due to a mucormycosis with Apophysomyceselegans.[94]

11.Pruritus

12.Pressure effect

Application of solid substance to the skin may produce an oedematous area which is most intense at the margins. This reaction is more common in persons who have a tendency to develop dermographism

13. Leakage of material on to the clothing, especially dyes

14. Folliclitis

16. Localized flare of dermatitis and other skin disorders

17. Generalised flare of dermatitis

18. Flare of dermatitis at previous contact site

19. Necrosis, scarring, and keloids

Hypertrophic scar formation is a rare complication and it is usually associated with very strong patch test reaction.

20. Milia[93]

Angry Back Syndrome

During active dermatitis uninvolved skin also exhibits increased susceptibility to irritant reactions which lead to multiple false positive patch test reactions that is ‘eczema creates eczema.’ It is also known an excited skin syndrome or crazy back syndrome[93]

Spot tests

1. Acetylacetone method for formaldehyde

Reagent :15 g of ammonium acetate + 0.2 ml of acetyl acetone+0.3 ml of glacial acetic acid in 100 ml of distilled water. This reagent should be stored in a refrigerator. The test product is put in a disposable glass test tube and 2.5 ml of the reagent is added. The mixture is shaken and then placed in a water bath at 60 degree C for 10 min. If formaldehyde is present yellow colour will be produced.[95]

2.Dimethyl glyoxime is used for nickel spot test.

Migration inhibition test, lymphocyte transformation test and leukocyte procoagulant activity are the invitro tests used to detect contact allergy.

Open Tests

The liquid test substance is applied on the skin (1cm area) and it is allowed to dry. Then reading will be taken at 48 hours and 72 hours. The risk of severe reactions is less, so it is mainly used as a screening procedure for less well known substances.

Usage Test`

If an open patch test or closed patch test is negative but patients history suggests a contact dermatitis we can perform usage test.

Repeated Open Application test (ROAT)

The test substances are applied twice daily for up to 28 days or until an eczematous reaction develops. The preferred test site is the upper arm or flexor surface of the forearm. An area of five cm2 should be employed.[96]

Intradermal Tests

Intracutaneous tests have been performed with simple chemicals, but it is mainly used for investigational purposes. This technique has proved reliable for nickel and corticosteroid allergy.[97]

Leg Ulcer Series Allergens

01. Control

02. Amerchol L 101

Amerchol is a trade name of product containing lanolin alcohol. It is obtained from hydrolysis of lanolin. Amerchol L 101 is a concentrated absorption base composed of lanolin alcohols and mineral oil.

Amerchol is an emulsifier and emollient in cosmetic and pharmaceutical bases, topical drugs. It is also found in furniture polish, leather, metal corrosion prevention, paper inks, textiles, furs, cutting oil and waxes.

Because of its ability to penetrate the epidermis to the depth of the stratum granulosum and into the keratinocytes, lanolin has been prescribed for the treatment of many skin conditions, including xerosis, eczema and nipple eczema in lactating women

Mortenson conducted a study, in this study 899 patients were patch tested with wool alcohols, hydrogenated lanolin, Eucerin, and AL-101.[98]out of 899 patients, 6.7% of patients were positive to at least one of these allergens. A Belgian study showed contact allergy to Amerchol L 101.[99]

Cross Reaction

Wool alcohols, Lanolin, Wool fat

Other names: Lanolin alcohol, Wool alcohol

Lanolin Paradox

In 1996, Wolf used the term "lanolin paradox".

1. Medicaments containing lanolin may sensitize patients, especially those with eczema ,whereas lanolin-containing cosmetics are less sensitizing.

2. Lanolin –containing medicaments will cause contact allergy when applied to ulcerated skin, but those same patients can not develop reaction to lanolin-containing cosmetics.

3. Lanolin-sensitive patients have negative patch-test reaction to pure lanolin: this can be due to a low concentration of allergens.

4. Wolf concluded that using only a paraben mix is not a reliable method to test for paraben contact allergy, the use of only 30% wool alcohol to test for allergy to lanolin is insufficient[100, 101]

03. Fusidic acid sodium salt:

Fusidic acid sodium salt is an antibiotic agent used in the treatment or prevention of cutaneous infection. It is mainly used for staphylococcal infection.

Sensitization to fusidic acid sodium salt may occur from its use on stasis ulcers. DeGroot reported a case of stasis ulcer with allergic contact dermatitis due to topical treatment with sodium fusidate ointment[102]

It is a bacteriostatic antibiotic which inhibit protein synthesis. Fusic acid sodium salt 2% in petrolatum is used for patch testing.

Indian brand names:

1. Fucidin cream/ointment - fusidic acid
2. Fucibet cream - fusidic acid + betamethasone
3. Bactirest-M cream - fusidic acid +mometasone furoate
4. Metos F ointment - fusidic acid + mometasone furoate
5. Fuzap cream - fusidic acid
6. Foban ointment - sodium fusidate
7. Fusic cream - fusidic acid
8. Clonate-F cream - clobetasol + fusidic acid
9. Fucidin- H cream – fusidic acid + hydrocortisone acetate

04. Chlorhexidine digluconate

Chlorhexidine chemical structure is 1.1-hexamethylene bis 5(P chlorophenyl) biguanide. It is an antibacterial compound. It is active against gram positive and gram negative bacteria even in the presence of body fluids.

Most frequently used chlorhexidine salts are digluconate, acetate, and diacetate. Nepal is the first country in the world to use topical Chlorhexidine.

Chlorhexidine is used as a surgical scrub, hand rinse and topical antiseptic. It should be used with caution on wounds caused by disturbed circulation.

The use of chlorhexidine on mucous membranes has been discouraged as it poses a risk of anaphylaxis. A woman cut her foot on broken glass. She applied a chlorhexidine disinfectant to the broken skin site. Within a minute she had urticaria, angioedema, wheezing, dizziness, vomiting and diarrhoea.

Urticaria and dyspnoea can occur if it is used for insertion of an intrauterine device.[103]

Chlorhexidine is biologically allergologically active in aqueous solutions only. So false negative patch test was obtained when chlorhexidine was applied in petrolatum. The ideal test for chlorhexidine is uncertain.

Chlorhexidine digluconate brands in India

1. Aloederm –B cream - Chlorhexidine Gluconate, Allantoin, Aloe Vera, Silver Sulphadiazine,

2. Savlon liquid – Chlorhexidine + cetrimide

3. Silverex cream – silver sulphadiazine gluconate+ chlorhexidine

4. Quadragel- lidocaine +metronidazole+chlorhexidine

5. Bactigauze plus dressing – chlorhexidine+silver sulphadiazine

6. Burnheal ointment 7.C.S.S cream 8.Clohex plus -mouth wash 9.Drez-S dressing 7.Heelcare cream 8.Metro gel 9.Orahex gel 10.Microgard Tulle 11.Silivindon plus cream.

05. Benzalkonium chloride

Benzalkonium chloride is a mixture of alkyl dimethyl benzyl ammonium chlorides. It is a quaternary ammonium cationic detergent. It is used as a preoperative skin disinfectant, for disinfecting surgical instruments.

Benzalkonium chloride is also used in the treatment of burns, ulcers, wounds, and infected dermatoses. It is found in many cosmetics, deodorants, dentifrices, mouth washes, lozenges and ophthalmic preparations.

It is used in the fabrication of textiles and dyes and in metallurgy and agriculture. It can cause cutaneous and mucous-membrane allergic contact dermatitis.

Lovell and Staniforth reported a case of allergic contact dermatitis due to the presence of benzalkonium chloride in plaster of paris.[104]

Cross reactions: cetrimonium bromide, benzethonium chloride.

Benzalkonium brands in India

1. Happynap cream- bezalkonium chloride+zinc oxide
2. Oilatum plus lotion – light liquid paraffin+BZK
3. Rashfree cream – zinc oxide + BZK
4. Bonzela ointment-choline, salicylate, lignocaine, BZK
5. Lacrisan eye drops-povidone iodine+ BZK
6. Orex cream- tannic acid+menthol+choline salicylate+BZK
7. Ulceheal gel-choline salicylate + BZK.
8. Ofelder eye/ear drops-ofloxacin +methyl cellulose+BZK

06. Nitrofurazone

Nitrofurazone is a topical antibiotic. It is also used in animal feeds and in veterinary medicine. It is available as nitrofurazone dressing, soluble powder and topical cream. Nitrofurazone is globally banned but it is available in India.

Nitrofurazone is a well known sensitizer. It is used extensively. It can cause severe allergic contact dermatitis. Patient who had ulcer with stasis dermatitis are particularly prone to sensitization.[105]

In one study 58 patients were sensitized by medicaments containing 0.2 % nitrofurazone. Most of the patients had stasis dermatitis or ulcer and re exposure to nitrofurazone had caused a generalized eczema in some patients.

Nitrofurazone soluble dressing can also produce allergic contact dermatitis when it is applied to a second degree burns of the leg..Nitrofurazone dressing and powder contain polyethylene glycols. Allergic reactions may occur either from nitrofurazone or the polyethylene glycols.

Nitrofurazone brands in India

Furacin ointment, Furacin cream, Furacin powder, Furacept cream, Decain cream, Emfurazone cream, Furocid ointment, Nitrofurazone gauze dressing, Nitraheal TM dressing.

07. Bacitracin

Bacitracin is a polypeptide antibacterial agent. It is produced by the Tracey 1 strain of Bacillus subtilis. It inhibits bacterial cell wall synthesis. It is active against gram positive organisms and spirochetes. It can be combined with polymyxin B, neomycin to provide a wide spectrum of bacterial coverage.

Adverse effects due to topical application of bacitracin are localized itching and burning. It is a frequent allergen in patients with chronic stasis dermatitis and conjunctivitis.

Bacitracin is a sensitizer. Topical application can produce anaphylactic shock. Polymyxin B sulphate can cross react with bacitracin, because both antibiotics are obtained from Bacillus subtilis. Bacitracin can “co-react” with neomycin. Most of the topical bacitracin preparation contains neomycin and Polymyxin.

Bacitracin(Indian Brands)

- Derbec-N cream – beclomathasone dipropionate + neomycin sulphate + bacitracin
- Nebaspor ointment and powder – polymyxin + bacitracin + neomycin sulphate
- Nebasulf skin ointment
- Neosporin powder, Neosporin skin ointment –polymyxin +bacitracin + neomycin sulphate
- Neosporin –H ointment
- Neotop powder -Bacitracin Zinc+ Neomycin Sulfate + Sulfacetamide
- Polybanetm tulle dressing–polymyxin + bacitracin + neomycin sulphate

08. Cetyl Stearyl Alcohol (Lanettee O)

Chemical formula for cetyl alcohol is CH3 (CH2)14 CH2 OH and for stearyl alcohol is CH3 (CH2)16CH2 OH. Both alcohols are often used together. They are used as an emulsifier and stabilizer

Both alcohols 50/50 are used as an emulsifier and emollient in cosmetic lotions, creams, ointments and pharmaceutical preparations.

Persistent urticarial plaques are the morphological presentation of chronic dermatitis. Cetyl stearyl alcohol can cause persistent urticarial plaques. Contact allergy is rare with this compound.

Usually there should be a predisposing factor that increases patient sensitivity. One patient had developed contact allergy to stearyl alcohol in 5 –fluorouracil cream. This is due to irritant effect of 5 –FU which predisposed to ACD develop.[106]

Sources

Moisturisers, antifungal, acne and steroidal creams, sunscreen, medicinal soaps, detergents, textile oils.

Example (Indian brands)

1. **Moisturizers**

   Cetaphil lotion and cream, Cetaphil cleansers, Cetaphil moisturizers, Cetraben cream, Dermadew lotion,Venusia max,Papulex cream.

2. **Antifungal Cream**

   Candid cream

   Nizoral cream

3. Topical Steroids

- Betnovate C and N creams –betamethasone valerate.
- Betnovate lotion
- Elocon cream-momatesone furoate
- Momate ointment
- Fucidin H cream and ointment –fusidic acid+hydrocortisone

09.2,6 Ditert-butyl 1-4-cresol (BHT)

2,6 Ditert-butyl-4-cresol is a butylated hydroxyl toluene. It is one of the most commonly used antioxidants in both foods and topical preparations. It is also used in the production of petroleum based products (eg.plastic, rubber, and fuels), as well as in animal feeds.

BHT has antibacterial effects; particularly active against corynebacterium sp. Prevalence of allergic contact dermatitis due to this agent is low.

Indian brands with BHT

Atlargo ointment – BHT +retapamulin

Tretin cream – tretinoin cream

10. Chloramphenicol

Chloramphenicol is an antibiotic and anti rickettsial substance produced by streptomyces venezuelae. It is act as bactericide against the rot of potatoes and other root vegetables.

One patient had two episodes of contact conjunctivitis and dermatitis of the lids due to application of chloramphenicol eye drops.[107]

Allergic contact sensitivity to this antibiotic is rare. Schwank and Jirasek reported contact allergy to chloramphenicol applied to stasis ulcers and eczemas. It can cross react with Azidamphenicol.

Chloramphenicol (Indian brands)

Chloromycetin drops, Dexamon drops, Solubin-c ointment, Chlorocol eye ointment.

11. Benzoyl peroxide

Benzoyl peroxide is used for treatment of leg ulcer. It may cause discoloration of hair.[108] It will mainly cause irritant reactions. allergic reaction to this agent is rare.

It is used to bleach candles white. It is an air borne contact ant. Exposure to burning candles in a church has caused facial dermatitis.

Benzoyl Peroxide Uses

1.Topical acne preparation

2.Additive to self-curing acrylic

3.Bleach for flour and oil

4.Stasis ulcer treatments

Acne preparation brands in India

Benzac AC gel, brevoxyl gel, pernox gel, persol gel.

12. Propylene Glycol (Pg)

Propylene glycol is a dihydric alcohol,CH3CHOHCH2OH. It is an odourless, viscous liquid. It is readily miscible with water, acetone, chloroform and essential oils.

PG is stable under ordinary conditions. It is very hygroscopic, with an isotonic concentration of 2% in water. It is used as a vehicle for topical therapeutics, cosmetics, and body lotions.

It is an antibacterial and antifungal. It acts against Escherichia coli, Pseudomonas and other bacteria, as well as Candida albicans, Bityrosporum orbiculare and some Dermatophtes. PG does not cause follicular hyperkeratosis and is therefore non comedogenic.[109]

PG is also used in automotive brake fluid and antifreeze formulations, alkyd resin manufacture, as a plasticizer for some resin systems. It is a solvent ,

humectants, inhibitor of fermentation, preservative, softening agent and a heat –transfer fluid for the processing of foods.

Undiluted Propylene glycol can be a skin irritant. Irritant effects of PG are more on atopic patients and those who have eczematous dermatitis. Irritant response to PG may be more frequent in winter.

Most of the steroid preparations contain PG to enhance the penetration and thus the efficacy of the corticosteroids. It is also used as a preservative in topical preparations.

Examples of Indian brands which contain propylene glycol

1.Moisturizers

Cetaphil lotion, venusia max, venusia lotion, venusia cream, dermadew lotion, moisture cream

2.Antifungal

Nizral cream

Onabet lotion.

3.Topical Steroids

Momate ointment

4.Sunscreen

Ansolar sunscreen

13. Propolis (bee glue)

Propolis is a dark yellow-brown resinous substance found in beehives. It is collected by bees from poplar buds. It contains cinnamic acid and vanillin which is known sensitizers.

It is used in the treatment of leg ulcer because it composed of a mix of essential oils, pollens and a variety of polyphenolic compounds (flavonoids, phenolic compounds). Polyphenolic compounds are antioxidants.

It is found in bio cosmetics, face creams, ointments, lotions, solutions, varnish, toothpaste, mouthwashes, tablets, chewing gums. It is also found in wax for violins. It is used in homeopathic medications.

Propolis may cross react with balsum of Peru. Allergic contact dermatitis due to propolis is an occupational hazard for beekeepers.

Cross reaction: Balsum of peru.

14.Thiomerosal (merthiolate)

Thiomerosal is an organic mercurial compound. It is used as an antiseptic .It is also used as a preservative in topical medicaments, contact lens solutions, eye drop solutions, cosmetics and vaccines. Thiomerosal contains two distinct radicals: an organic mercury compound and a thiosalicylate. Thiosalicylate compound is a strong sensitizer.

It is used as a preservative in vaccines, antitoxins, parentral medications, and diluting fluids used for preparation of antigens for scratch or Intradermal testing. Thiomerosal can produce life –threatening reactions. Thiomerosal is commonly found in hepatitis, tetanus and meningoencephalitis vaccines.

Thiomerosal sensitive patients can be divided into three groups:

1. Positive to Thiomerosal but negative to thiosalicylic acid and to other mercury compounds.
2. Positive to Thiomerosal and to some other mercury compounds. But negative to thiosalicylic acid
3. Positive to thimerosal and to thiosalicylic acid but negative to other mercury compounds

Thiomerosal is used as a preservative in contact lens solution and eye drop solution which can cause conjunctivitis and eyelid dermatitis. In one instance, a sensitized person had hand dermatitis without conjunctivitis.

A patient with Thiomerosal sensitization had developed allergic contact dermatitis over the fingers and palms; however when this same solution was applied to the eyes, it did not produce eye lid dermatitis.[110]

Cosmetic products with thimerosal

Fair & Lovely, Fair & Handsome, GarnierLite, Olay- products with thiomerosal.

Indian brands with thiomerosal

Vaccines

Tripedia –DTaP vaccine

Fluzone –seasonal trivalent influenza vaccine

TT vaccine.

15.Sorbic Acid

Sorbic acid chemical name: 2,4-hexadienoic acid and 2-propenyl – acrylic acid.

Chemical formula : C6H8O2

Sorbic acid is obtained from the berries of the mountain ash, Sorbus aucuparia, L.rosaceae. It is found incranberries, strawberries and is used as a preservative in many foods.

It is used as a preservative in cosmetic and pharmaceutical products. It is also used in alkyl coating and drying oils, adhesives, glues, inks, paints, varnishes, tanning agents, metal working fluids.

It is a white, odourless, crystalline powder with a faintly acid taste. Potassium sorbate is a salt form of sobic acid. It is also a white odourless powder. It is soluble in water, alcohol and propylene glycol. It has excellent fungi static activity and with little antibacterial activity.

Allergic contact dermatitis due to sorbic acid is rare. Clemmensen and Schiodt reported that sorbic acid in the particular concentration, when used as a preservative is not urticariogenic.[111]

Allergic reaction can occur if it is inhaled, ingested or in contact with skin. Inhalation of pure sorbic acid should be considered as a medical emergency.

Sorbic acid can produce an immediate nonspecific erythema. topical agents that can produce immediate nonspecific erythema include benzoic acid, sodium benzoate, MP, cinnamic aldehyde, cinnamic alcohol and ethyl vanillin.

Cross reaction : potassium sorbate.

Potassium sorbate containing preparations

Nizral cream- ketoconazole cream

Pramosone cream-hydrocortisone cream

Fucidin H cream –fusidic acid + hydrocortisone

16.Eosin

Eosin is a red dye belonging to the xanthenes group. Back in 1920-30s it was used in high concentrations in lipsticks. It is also used as a colouring agent in nail polish, wool. Silk and paper. It is now approved by the FDA for use in inks.

17.4-chloro-3-cresol

Chemical formula:C7-H7-CL-O

Chemical name:4-chloro-3-methylphenol

Chlorocresol is a chlorinated phenol. It is used as an antiseptic agent, disinfectant, antifungal agent and anti- bacterial agent. It is also used as a preservative for various creams, lotions, cosmetics, glues, gums, paints, inks, textiles and leather goods.

Chlorocresol is found as white or slightly pink dimorphous crystals that have a phenolic odor. It is toxic to wild life, water –dwelling organisms. It is active against gram positive and gram negative bacteria, fungi but little activity against bacterial spores except at high temperature.

It is more active in acid than in alkaline solution. It can cross react with parachlorometaxylenol. chlorocresol is an infrequent sensitizer. Of 1000 patients who had contact dermatitis analysed by burry and colleagues, only 11 patients reacted to chlorocresol.[112]

Dermatitis from chlorocresol in betamethasone creams were reported in 13 patients.[112]

Chlorocresol in Indian creams

1.Topical Steroid Creams

- Tenovate cream- clobetasol propionate
- Eumosone cream-clobetasone

- Betnovate-N cream, betnovate–M cream, Betnovate-GM cream, betnovate-C cream
- Betanil cream-betamethasone
- Bactoderm –N cream –betamethasone +neomycin
- Clonate –G cream – clobetasol+gentamycin
- Cosvate-GM gel- clobetasol+gentamycin
- Sonoderm – M cream-clobetasol+ micanozole
- Fucibet cream –fusidic acid +betamethasone valerate
- Anovate cream – beclomethasone dipropionate+phenyl ephrine hydrochloride.

Topical corticosteroid cream free of chlorocresol

- Dexomet cream - desoximetasone
- Flutivate cream -fluticasone
- Momate –F cream –mometasone
- Halox cream – halobetasol propionate

18. Budesonide

Budesonide is a non- halogenated corticosteroid. It used in topical preparations. It is a good marker of wide range of cortisone allergy.

Coopman classification of corticosteroids based on frequency of cross reactivity

Class A

Hydrocortisone type

Ex. Hydrocortisone with C17 and/or C21 –acetate,tixocortol pivalate, prednisone+/-acetate, methyl prednisolone+/- acetate

Class B

Triamcinolone type

Ex.Triamcinolone acetonide or alcohol, budesonide, desonide, halcinonide, amcinonide

Class C

Betamethasone type (not valerate)

Ex.betamethasone and disodium phosphate, dexamethasone and disodium phosphate, desoximetasone

Class D1

Less labile

Ex.Clobetasol propionate and butyrate, betamethasone valerate and dipropionate, mometasone furoate, beclomethasone dipropionate

Class D2

More labile

Hydrocortisone -17-butyrate and 17-aceponate and 17-buteprate, Prednicarbate.

Rim reaction or edge effect

Erythema occurs only around the circumference of the chamber, represents true sensitization. This phenomenon is seen with corticosteroids.

Lauerma reported that classes A,B and D cross reacted most frequently and he proposed tixocortol pivalate and hydrocortisone-17-butyrate as a good screening combination. Class B rarely cross reacted with class C. Class C is the least common corticosteroid allergen in Finland.

Contact allergy to budesonide has been reported from nasal sprays and oral inhalers. A study of 30 patients on inhaled corticosteroids found that 2 patients were sensitized to budesonide[113]

Recommended concentration for patch testing with budesonide is 0.1% in petrolatum. budesonide sensitized patient should avoid triamcinolone, amcinonide, fluocinolone acetonide, halcinonide, flucinonide,desonide and any others that end with the letters "….ide".

Budesonide Indian brand name

Budesal respules,budecort respules,budenase AQ spray,budecort neohaler,foracort rotacap,rhinocort rota cap,combihale –FB inhaler

18. Triethanolamine

Triethanolamine is also known as trolamine or TEA. It is a mixture of three alkanolamines. It is used frequently as an excipient in body lotions, shaving creams, soaps, shampoos, bath powders, and pharmaceutical preparations.

Excipient : An inert substance that gives a topical preparation proper consistency by its action as a dispersant or detergent. Excipient should have no pharmacological action by themselves, but may cause allergic reaction in sensitive individual.

Castelain reported allergic contact dermatitis due to sensitization to TEA. Triethanolamine can cross react with phenergan.[114] It is a more common sensitizer in industrial products than in cosmetic products. In one patient, a fluorescent marking pen used in patch testing caused allergy from triethanolamine

Triethanolamine containing products

Sungrace and suncote gel - sunscreen

Acnemoist - moisturiser

Dermadew lotion – moisturiser

20. Framycetin Sulphate

Framycetin is a broad spectrum aminoglycoside antibiotic. It is usually bactericidal in action. Although the exact mechanism of action has not been

fully elucidated, the drug appears to inhibit protein synthesis in susceptible bacteria by binding to ribosomal subunit (30s protein).

Framycetin is active against many aerobic gram-negative bacteria and some aerobic gram-positive bacteria. It is inactive against fungi, viruses and most anaerobic bacteria.

It is a component of neomycin that is produced by streptomyces fradiae. On hydrolysis framycetin yields neamine and neobiosamine B .

Indications

- Pyoderma,folliculitis,paronychia,sycosis barbae,impetigo
- Also useful in controlling secondary bacterial infection in skin carcinoma,eczema,contact dermatitis,seborrhea,acne,psoriasis,varicose ulcer and neurodermatitis
- Treatment of blepharitis,conjunctivitis,styes,corneal abrasions,burns.

Framycetin sulphate Indian brand names

- Proctosedyl ointment.2.sofradex cream 3.sofradex-F cream4.sofracort drop5.soframycin cream 5.sofra-Tulle 6.famitulle antibiotic dressing.

Cross reaction:

Neomycin, Parommycin, Kanamycin.

21. Sorbitan Sesquioleate

Sorbitan sesquioleate is derived from monoesters and diesters of oleic acid and hexitol anhydrides of sorbitol. It is a common non-ionic emulsifier.

Case reports have described contact allergy to both sorbitan sesquioleate and Sorbitan monoleate. Contact dermatitis from Sorbitan sesquioleate has been reported to be caused by wound dressings and a topical corticosteroid preparation (patch-test concentrations of 20% and 10% in petrolatum, respectively).[115]

A case series of children also noted contact allergy to Sorbitan sesquioleate (20% in petrolatum) in certain paediatric products as well as in topical corticosteroid preparations.[116]

Case reports have reported that patients with leg ulcers had positive patch-test reactions to Sorbitan sesquioleate 2% in petrolatum, Sorbitan monoleate 2% in petrolatum, and Sorbitan monoleate 20% in petrolatum.[117]

A larger series of 23 leg ulcer patients found that 17% were allergic to Sorbitan monoleate (10% petrolatum) and that 13% were allergic to Sorbitan sesquioleate (20% petrolatum).[118]

Indian brands with sorbitan sesquioleate

Pramosone cream and ointment - topical steroid

22. Tixocortol-21-pivalate(pivalone)

Tixocortol-21-pivalate is a class A (hydrocortisone type) corticosteroid. It is most sensitive and specific marker for hydrocortisone contact allergy. It is mainly used for contact dermatitis screening rather than treatment.

Patients with tixocortol-21-pivalate allergy should avoid hydrocortisone, prednisone, prednisolone and methlprednisolone. Dexamethasone and betamethasone are safer internal corticosteroids in these patients.

23. Sorbitan Monoleate

Sorbitan monoleate is a monoester of oleic acid and hexitol anhydrides derived from sorbitol. It is used as a emulsifier in cosmetic and pharmaceutical ointments and creams. It can cross react with sorbitan sesquioleate.

24. Phenyl mercuric acetate

Chemical formula: C8H8HgO2

Phenyl mercuric acetate is an organo mercurial derivative. It is used as a bacteriostatic agent. It is also used as a preservative in antibiotic eye drops and cosmetics. Systemic administration of medication containing mercury can cause allergic contact dermatitis in sensitized persons. It is used in contraceptives, antifungal agents, shoe linings, shampoos and emulsion paints.

Cross reaction

Organic mercuric compounds: phenyl mercuric borate and phenyl mercuric nitrate.

Inorganic salts: ammoniated mercury and bichloride of mercury.

Indian brands with phenyl mercuric acetate

Betal –N drops – betamethasone +neomycin

betnor drop – betamethasone.

25.Chloroacetamide

Chemical formula: C2H4ClNO

Choloroacetamide is a water soluble preservative useful against yeast and fungi. It is used in cosmetic products, paints, shoes, adhesives and cutting oil. It is used as an intermediate in the production of herbicides and insecticides. Chloroacetamide is banned in France because chloroacetamide is a category 3 mutagenic or reproductive toxin.

Axillary dermatitis from a deodorant has been reported from Australia. Currently, patch testing is performed with chloroacetamide 0.2 % in petrolatum. one study from Swiss out of 2,295 patients only 1.5% of the patients showed chloracetamide sensitization.[119]

26.Diazolindinyl Urea

Chemical formula:C8H14N4O7

Diazolindinyl urea is a formaldehyde releasing preservative. It is produced by the chemical reaction of allantoin and formaldehyde in the presence of sodium hydroxide solution and heat.

It has antibacterial and antifungal action. It was introduced in 1982. It is used in cosmetic creams, lotions, shampoos and hair gels It is a stronger sensitizer than imidazolidinyl urea.

It is also known as Germall II. As per data collected from 2002-2004 NACDG, prevalence of contact allergy to diazolindinyl urea is 3.5%.[120] Cross-sensitivity between Diazolindinyl Urea and Imidazolidinyl Urea is common but does not always occur.

Five commonly used formaldehyde-releasing preservatives

1. Bronopol
2. Diazolidinyl urea
3. DMDM hydantoin
4. Imidazolidinyl urea
5. Quaternium- 15

Diazolidinyl urea containing preparations

- Acnemoist - moisturizer
- Papulex - moisturizer
- Suncote gel -sunscreen

27. Imidazolidinyl Urea

Imidazolidinyl urea is a formaldehyde releasing preservative. It is also known as Germall 115. It is one of the most commonly used cosmetic preservative after paraben. It is non-toxic, non-irritating, so it is compatible with almost all cosmetic ingredients. It is used as a preservative in lotions, creams, hair conditioners, shampoos, deodorants and topical drugs.

It is highly water soluble, colourless, odourless, tasteless and is not pH dependent. Imidazolidinyl urea is more active against bacteria than against yeast and moulds. It is active against both gram-positive and gram negative-organisms. In one case report, six out of fifteen imidazolidinyl urea sensitive patients reacted to formaldehyde.[121] Theoretically, imidazolidinyl urea releases about one-eighth as much formaldehyde as Quaternium-15.

It acts synergistically with other preservatives, particularly with the parabens, which results in wide range of antimicrobial coverage. In one study, out of 30 formaldehyde –allergic patient only one patient had reacted to imidazolidinyl urea, where as 9 reacted to quaternium -15.

Indian products with imidazolidinyl urea

Flutivate cream – fluticasone propionate

Tenovate GN cream – clobetasol propionate+neomycin

28. Wood Tar Mix

Wood tar mix include pine tar, beech tar, juniper tar (oil of Cades) and birch tar(oleum rusci). They are used in shampoos, deodorants, cough syrups, counter irritant veterinary liniments, tooth powders, disinfectants and insecticides.

Allergic reactions were found in only 1.8% of patients. Positive reaction to coal tar and wood tar are more frequent among balsum of peru sensitive patient. . Coal tars are phototoxic but wood tars are not phototoxic.

Tar

It is a dark-brown or black, viscid liquid obtained from various species of pine or from bituminous coal.

Juniper Tar (oil of cade)

It is a volatile oil obtained from wood of juniperus oxycedrus. Mathias and colleagues[122] reported that juniper tar is an irritant and it should be tested at half its commercial strength or at a low concentration.

Pine Oil

It is a mixture of terpene alcohols, hydrocarbons, and ethers. It can produce serious toxic effects if ingested or aspirated.

Birch Tar Oil (Oleum Rusci)

Rothenborg and Hjorth[123] reported that positive patch test reactions to a mixture of wood tars consisting of pine, juniper, beech and birch produce false-positive reactions. When a wood tar mix is positive, each tar should be tested individually.

TABLE -7

LEG ULCER SERIES ALLERGENS

S.NO	ANTIGENS	Group
1.	Control	-
2.	Amerchol L 101	Emollient Emulsifier
3.	Fusidic acid sodium salt	Antimicrobial agent
4.	Chlorhexidine digluconate	Antimicrobial agent
5.	Benzalkonium chloride	Disinfectant
6.	Nitrofurazone	Antimicrobial agent
7.	Bacitracin	Antimicrobial agent
8.	Cetyl stearyl alcohol (Lanettee)	Emollient Emulsifier Preservative
9.	2,6 Ditert-butyl-4-cresol(BHT)	Antioxidant Antimicrobial agent
10.	Chloramphenicol	Antimicrobial agent
11.	Benzoyl peroxide	Topical acne Preparations Treatment of leg ulcer.
12.	Propylene glycol	Vehicle for topical preparations Antimicrobial Antifungal Preservative
13.	Propolis	Cosmetic related to balsum of peru Treatment of leg ulcer
14.	Thimerosal(Meethiolate)	Preservative Antiseptic Excipient

15.	Sorbic acid	Preservative Antifungal
16.	Eosin	Topical antibacterial preparation
17	4-Chloro-3-cresol(PCMC)	Preservative Antiseptic Anti bacterial Disinfectant Antifungal Excipient
18	Budesonide	Corticosteroid
19	Triethanolamine	Excipient
20	Framycetin sulphate	Antibacterial
21	Sorbitan sesquioleate	Excipient Emulsifier
22	Tixocortol-21-pivalate	Corticosteroid
23	Sorbitan monoleate(span 80)	Emulsifier
24	Phenyl mercuric acetate	Preservative Bacteriostatic agent
25	Chloroacetamide	Preservative Antifungal
26	Diazolindinyl urea(Germall ii)	Preservative Antifungal Antibacterial
27	Imidazolidinyl urea(Germall 115)	Preservative Antifungal Antibacterial
28	Wood tar mix	Fragrance, plant extract.

MATERIALS AND METHODS

MATERIALS AND METHODS

Study design

This study was done as a hospital based descriptive, observer blinded study

Study Population

Chronic leg ulcer patients aged 18 years and older, male or female, attending the Dermatology OP were included in the study. A total of 50 patients with chronic leg ulcers with or without surrounding dermatitis due to various causes is selected.

Study Period

This study was done during a period of 18 months after obtaining clearance from the ethical committee. Written informed consent was taken from all patients involved in our study.

Inclusion Criteria

-50 chronic leg ulcer patients with or without surrounding dermatitis were included in this study.

Exclusion Criteria

1. Patients are having acute skin eruptions on the back.
2. Patients are taking oral corticosteroids more than 20mg per day.
3. Patients on any other immunosuppressant's
4. Pregnant and lactating mother
5. Age <18 years

Methods

- 50 patients with chronic leg ulcer were recruited and informed consent was obtained.
- Detailed history and clinical examination was performed (enclosed in proforma)
- The leg ulcer series is obtained from chemo technique which consists of 28 allergens. These allergens were applied on finn chambers and were strapped to the back of the patients with tapes.
- The patches must stay in place undisturbed for at least 48 hours. vigorous exercise, stretching, shower and sun light exposure should be avoided.
- After 48 hours, the finn chambers were removed and the squares representing each chamber were marked using a marker pen.
- Readings were taken after half an hour and again second reading were taken at 72 hours.

INTERPRETATION OF THE RESULTS

The patch test results were scored using the International Contact Dermatitis Research Group grading

Table - 8

ICDRG CRITERIA

Score	Reaction
− (0)	Negative
? +	Doubtful reaction; faint erythema only
+	Weak positive reaction; palpable erythema, infiltration, possibly papules
++	Strong positive reaction; erythema, infiltration,papules,vesicles
+++	Extreme positive reaction; intense erythema and infiltration and coalescing vesicles
IR	Irritant reaction of different types
NT	Not tested

TABLE - 9

LEG ULCER SERIES

S.No.	ANTIGEN	%	Vehicle
01	Control		
02	Amerchol L 101	50	Pet
03	Fusidic acid sodium salt	2	Pet
04	Chlorthexidine digluconate	0.5	Aq
05	Benzalkonium chloride	0.1	Aq
06	Nitrofurazone	1	Pet
07	Bacitracin	5	Pet
08	Cetyl Stearyl alcohol (Lanettee O)	20	Pet
09	2,6 Ditert-buty1-4-cresol (BHT)	2	Pet
10	Chloramphenicol	5	Pet
11	Benzoylperoxide	1	Pet
12	Propylene glycol	5	Pet
13	Propolis	10	Pet
14	Thimerosal (Merthiolate)	0.1	Pet
15	Sorbic acid	2	Pet
16	Eosin	5	Pet
17	4-Chloro-3cresol (PCMC)	1	Pet
18	Budesonide*	0.01	Pet
19	Triethanolamine	2	Pet
20	Framycetin sulphate	20	Pet
21	Sorbitan Sesquioleate	20	Pet
22	Tixocortol-21-pivalate	0.1	Pet
23	Sorbitan Monoleate (Span 80)	5	Pet
24	Phenyl Mercuric acetate	0.01	Aq
25	Chloroacetamide	0.2	Pet
26	Diazolindinyl urea (Germall II)	2	Pet
27	Imidazolidinyl urea (Germall 115)	2	Pet
28	Wood tar mix (Pine, beech, Juniper, Birch)	12	Pet

RESULTS

Table - 10

AGE AND SEX DISTRIBUTION

Age in years	Sex		Total	Percentage
	Male	Female		
10 - 20	0	0	0	0
21-30	5	0	5	10
31-40	5	3	8	16
41-50	4	1	5	10
51-60	7	1	8	16
61-70	12	4	16	32
71-80	4	0	4	8
81-90	4	0	4	8

Fig .4

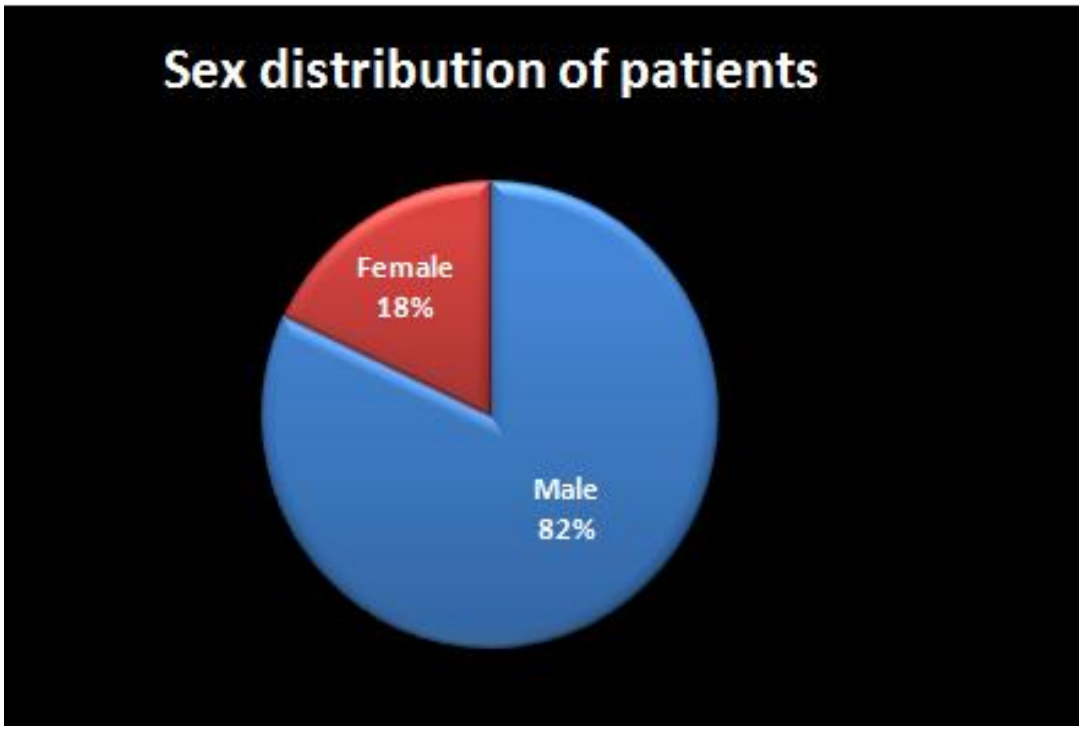

Sex distribution of patients
Female
18%
Male
82%

Fig 5

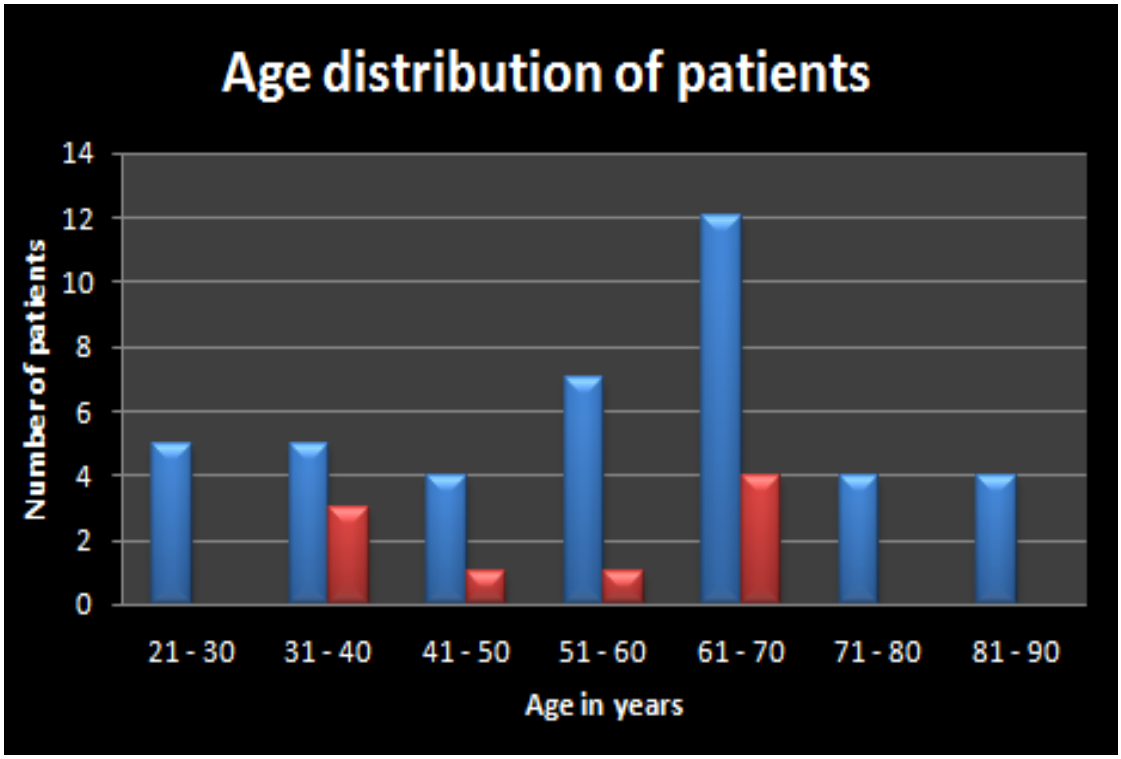

Age distribution of patients
Number of patients
0
2
4
6
8
10
12
14
21 - 30
31 - 40
41 - 50
51 - 60
61 - 70
71 - 80
81 - 90
Age in years

TABLE - 11

DURATION OF ULCER

Duration of ulcer in months	Number of patients	%	Number of patients with positive patch test	%
0-3	17	34	14	82.4
3-6	12	24	7	58.3
6-12	7	14	5	71.4
12-60	8	16	5	62.5
>60	6	12	5	83.3

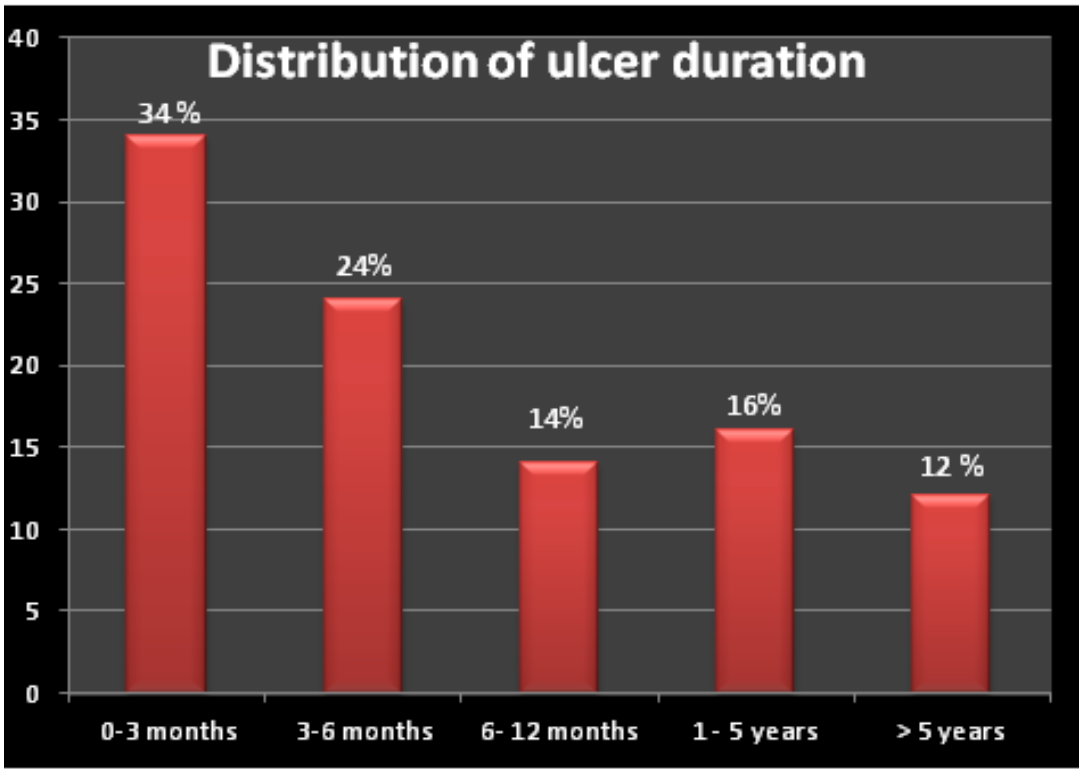


Fig .6

Table - 12

OCCUPATION

S.No	Occupation	Number	Percentage
1.	Business	4	8
2.	Farmers	6	12
3.	Housewives	9	18
4.	Retired	6	12
5.	Un employed	9	18
6.	Nurse	1	2
7.	Teacher	2	4
8.	Labour	9	18
9.	Miscellaneous	4	8

Table – 13

HISTORY

S.NO	History	Number of patients – yes	Number of patients- No
1.	Varicose vein	24	26
2.	Claudication pain	4	46
3.	Rest pain	6	44
4.	Trauma	11	39
5.	Anaesthesia	5	45
6.	Diabetes	15	35
7.	Hypertension	10	40

Table - 14

PREVIOUS TREATMENTS (TOPICAL)

S.No	Topical preparations	Number of patients – Applied	Number of patients- Not Applied
1.	Emollient	26	24
2.	Antibiotics	30	20
3.	Steroid	23	27
4.	Antiseptic	7	43
5.	Combination	13	37

Table - 15

PREVIOUS TREATMENTS (SYSTEMIC)

S.NO	Systemic treatment	Number of patients- taken	Number of patients- not taken
1.	Antihistamines	13	37
2.	Antibiotics	30	20
3.	Steroids	6	44

Table - 16

RESPONSES TO TREATMENT

S.NO	Response to treatment	Number of patients
1.	Improved	21
2.	Not improved	24
3.	Worked	5

TABLE - 17

EXAMINATION FINDINGS

S NO	Examination findings	Present	Not present
1.	Varicose vein	22	28
2.	Deformities of limb	5	45
3.	Edema of leg	36	14
4.	Peripheral pulsation	46	4

EXAMINATION FINDINGS

TABLE -18

EXAMINATION OF (ULCER) SURROUDING SKIN

S.NO	Surrounding skin	Present	%	Not present	%
1.	Pigmentation	38	76	12	24
2.	Indurations	25	50	25	50
3.	Dermatitis	40	80	10	20

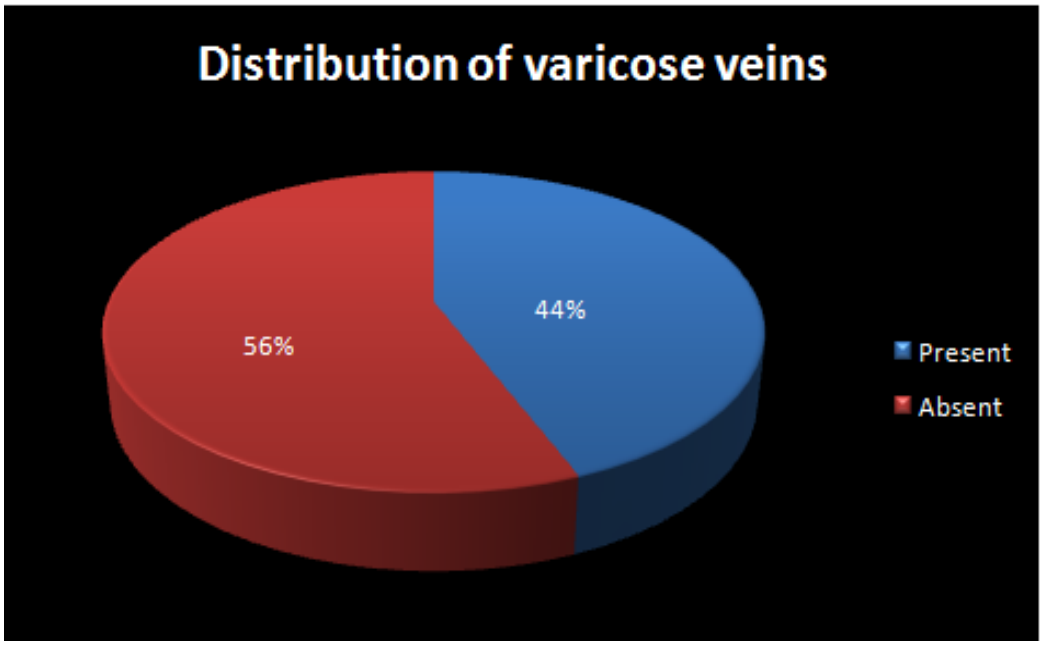


Fig 7

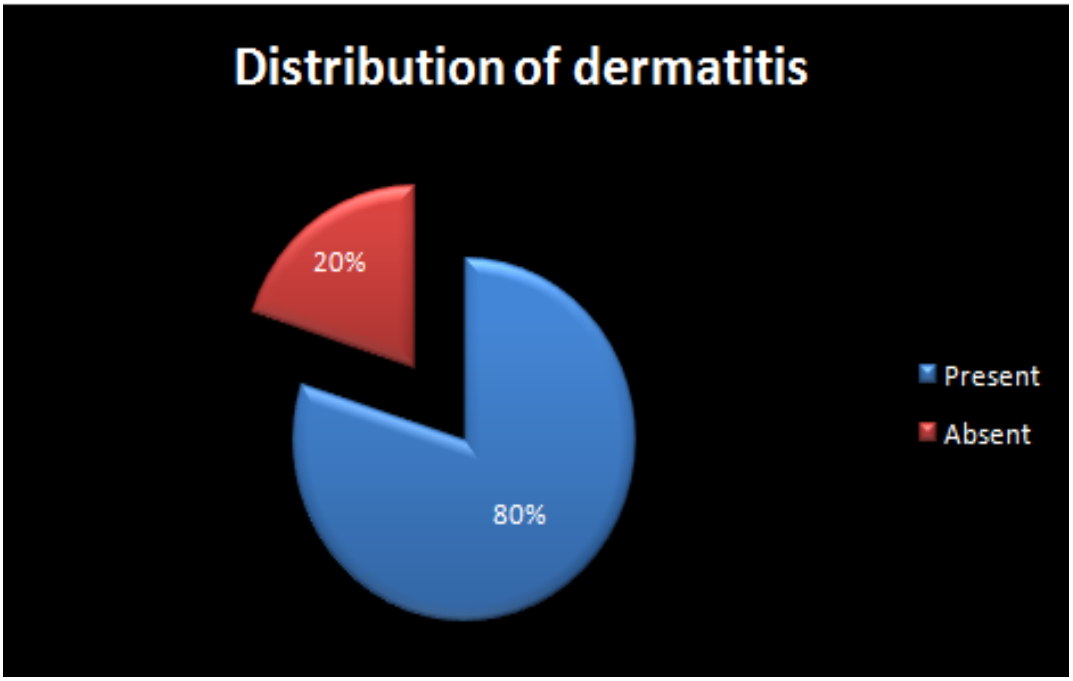


Fig.8

Table - 19

ULCER SITE

S.NO	Site	No of patients	%
1.	Lateral aspect of leg	2	4
2.	Medial aspect of leg	2	4
3.	Lateral malleolus	6	12
4.	Medial malleolus	16	32
5.	Plantar aspect	2	4
6.	Shin	2	4
7.	Dorsal aspect of foot	20	40

Table - 20

CAUSES OF LEG ULCERS

S.No	Causes for leg ulcer	No of patients	Percentage
1.	Venous ulcer	28	56
2.	Mixed ulcer	5	10
3.	Pyoderma gangrenosum	5	10
4.	Vasculitic ulcer	3	6
5.	Trophic ulcer	3	6
6.	Factitious ulcer	1	2
7.	Others	5	10

Table - 21

FREQUENCY OF ALLERGENS POSITIVITY

S.NO	Frequency of number of allergens positive	No of patients	%
1.	One allergen positive	7	19.4
2.	Two allergen positive	10	27.8
3.	Three allergen positive	10	27.8
4.	Four allergen positive	3	8.3
5.	Five allergen positive	3	8.3
6.	Six allergen positive	2	5.6
7.	Eleven allergen positive	1	2.8

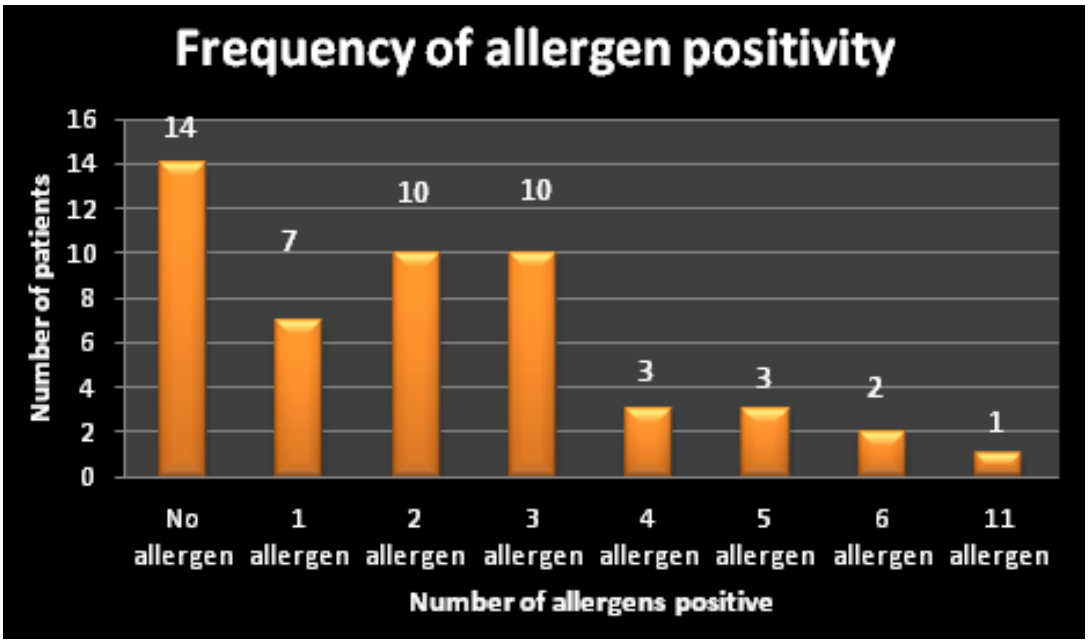

Frequency of allergen positivity
Number of patients
16
14
12
10
8
6
4
2
0
14
7
10
10
3
3
2
1
No allergen
1 allergen
2 allergen
3 allergen
4 allergen
5 allergen
6 allergen
11 allergen
Number of allergens positive

Fig.9

Table - 22

LEG ULCER SERIES ALLERGENS POSITIVITY

S.NO	ANTIGENS	NO OF PATIENTS (POSITIVE)	PERCENTAGE
1.	Control	0	0
2.	Amerchol L 101	3	8.3%
3.	Fusidic acid sodium salt	2	5.5%
4.	Chlorhexidine digluconate	4	11.11%
5.	Benzalkonium chloride	9	25%
6.	Nitrofurazone	1	2.78%
7.	Bacitracin	4	11.11%
8.	Cetyl stearyl alcohol(Lanettee)	3	8.3%
9.	2,6 Ditert-butyl-4-cresol(BHT)	1	2.78%
10.	Chloramphenicol	1	2.78%
11.	Benzoyl peroxide	1	2.78%
12.	Propylene glycol	5	13.89%
13.	Propolis	4	11.11%
14.	Thimerosal(Meethiolate)	9	25%
15.	Sorbic acid	2	5.5%
16.	Eosin	4	11.11%
17	4-Chloro-3-cresol(PCMC)	11	30.55%
18	Budesonide	1	2.78%
19	Triethanolamine	2	5.5%
20	Framycetin sulphate	10	27.78%
21	Sorbitan sesquioleate	2	5.5%
22	Tixocortol-21-pivalate	0	0
23	Sorbitan monoleate(span 80)	5	13.89%
24	Phenyl mercuric acetate	4	11.11%
25	Chloroacetamide	2	5.5%
26	Diazolindinyl urea(Germall ii)	2	5.5%
27	Imidazolidinyl urea(Germall 115)	4	11.11%
28	Wood tar mix	11	30.55%

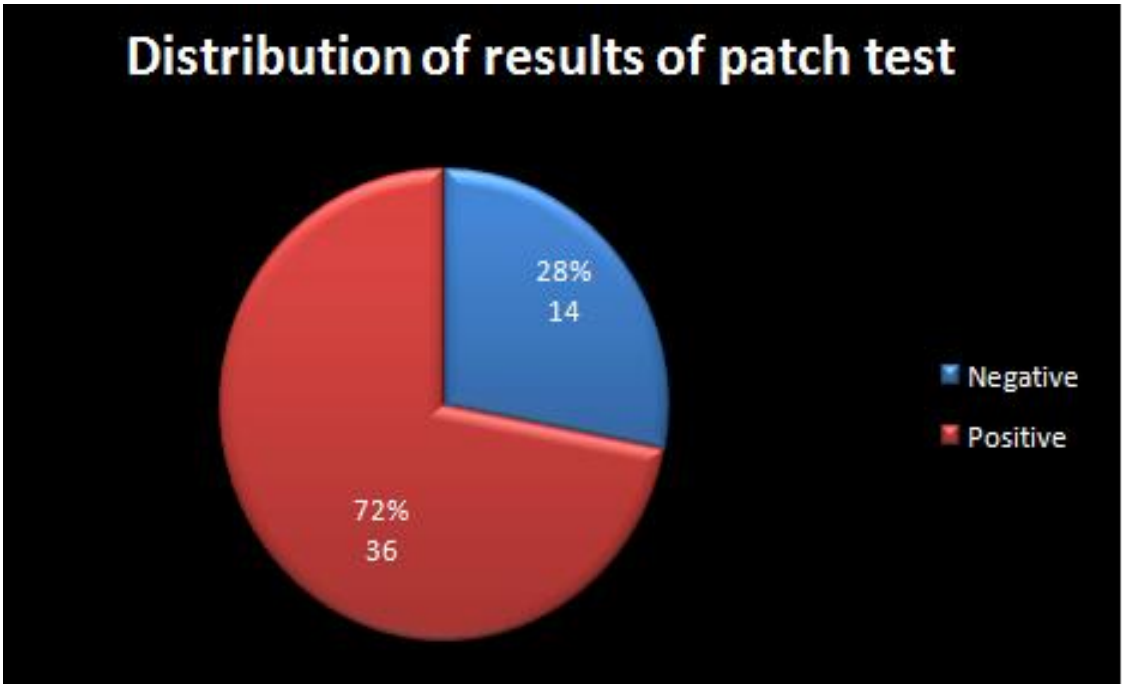

Distribution of results of patch test
28%
14
72%
36
Negative
Positive

Fig .10

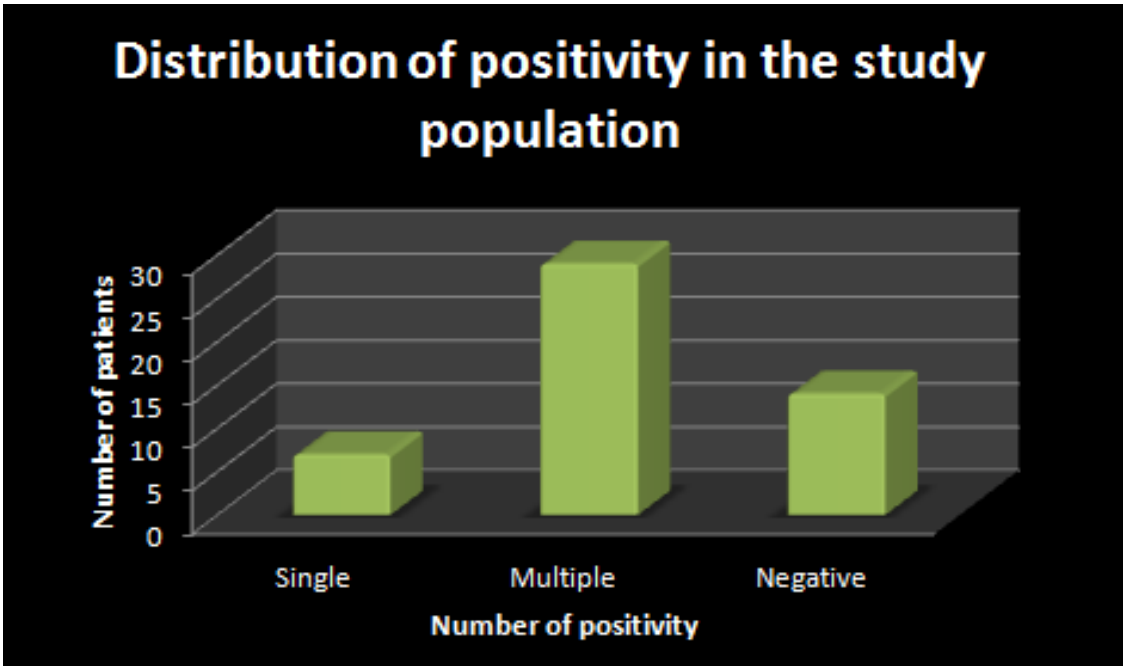

Distribution of positivity in the study population
Number of patients
30
25
20
15
10
5
0
Single
Multiple
Negative
Number of positivity

Fig 11

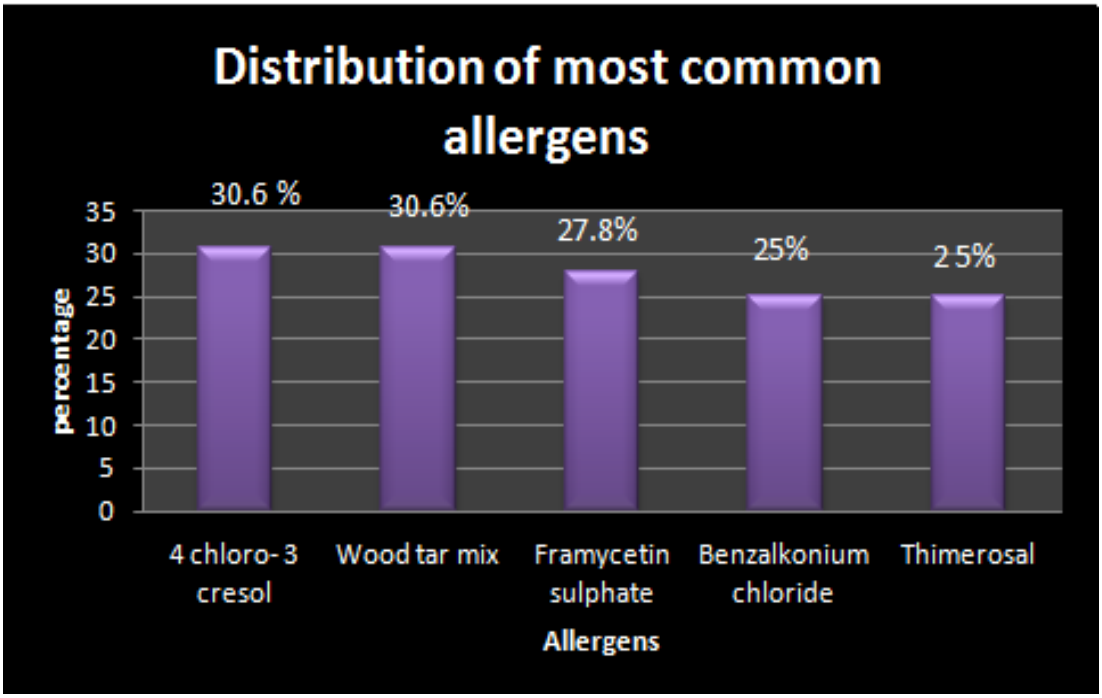

Distribution of most common allergens
30.6 %
30.6%
27.8%
25%
25%
35
30
25
20
15
10
5
0
percentage
4 chloro- 3 cresol
Wood tar mix
Framycetin sulphate
Benzalkonium chloride
Thimerosal
Allergens

Fig 12

DISCUSSION

DISCUSSION

In our study out of 50 patients, 41 patients were males and 9 patients were females. The duration of leg ulcers when patch tests were carried out was 0-3 months in 17 patients, 3-6 months in 12 patients,6-12 months in 7 patients,12-60months in 8 patients and >60months in 12 patients.

In our study ulcer duration was not associated with sensitization rate, but a number of European studies showed a significant correlation between ulcer duration and contact sensitization.[5]

From this study, we conclude that contact sensitization and polysensitization are very common in chronic leg ulcer patients. In our study 36 patients (72%) showed positive patch test reactions. Over all 14% had at least one positive reaction, 58% demonstrated 2 or more positive reactions in our study.

A North American study[7] reported prevalence of sensitization was 63% which was low compared with our study but another study[6] showed 80% positivity which was high compared with our study.

Out of 36 patients, 11 patients (30.5%) showed positive reaction to 4-chloro3-cresol and wood tar mix. 4-chloro-3-cresol and wood tar mix was the most common sensitizer in our study whereas western study showed only 2% chlorocresol positivity.[2] Although 4-chloro-3-cresol is an infrequent allergen in other countries, in India 4-chloro3-cresol positivity is high.

Since it is present in most of the corticosteroids creams, patients who have tested positive for chlorocresol should avoid steroid cream containing chlorocresol.

Various studies have reported chlorocresol sensitivity. Oleffe and colleagues reported allergic reaction to chlorocresol in corticosteroid creams.[124] Park in New Zealand reported a case who had allergy to chlorocresol in betamethasone cream.[125]

Of 1000 patients who had contact dermatitis analysed by Burry and colleagues, only 11 patients reacted to chlorocresol.[126] Dermatitis from chlorocresol in betamethasone creams was reported in 13 patients. (Burry and colleagues)[126]

Sensitization rates to wood tar mix as per various studies are 2.8% , 3.4%,4.5%,15%,20% and 21%,[7,127,128,129,130] but our study sensitization rate to wood tar mix (30.5%) was high comparatively.

Wood tar mix is not used in leg ulcer treatment, but it is found in many cosmetics and personal care products. It can also cross react with balsum of peru and fragrance mix. So high rate of contact allergy to wood tar mix could be due to cross reaction with this allergens.[7]

The second most common sensitizer in our study was framycetin sulphate. In contrast to other studies (39%, 7%)[2,7] our study 10(27.8%) patients showed positive reaction to framycetin sulphate.

The world literature series showing sensitization to neomycin and framycetin was around 12 to 16% from1975 to 2003.[131]

In India most of the topical antimicrobial creams contain framycetin and neomycin combination. It is usually combined with antifungals and steroids. So high incidence of framycetin positivity could be due to cross reaction with neomycin.

Cross reaction can occur between neomycin and framycetin because both groups contain neosamine sugar.[130]

The third most common sensitizers were bezalkonium chloride and thimerosal. Bezalkonium chloride is a disinfectant and thiomerosal is antiseptic and preservative.

In our study 9 patients (25%) showed positive reaction to benzalkonium chloride and thiomerosal whereas in western studies benzalkonium chloride contact allergy rates were 8% , 13%[7,130] and for thimerosal 4%,4%[7,130] which was low compared with our study.

Sorbitan monoleate and propylene glycol proved to be next most frequent sensitizers. Sorbitan monoleate is an emulsifier and propylene glycol is used as vehicle in various creams.

In India most of the emollients and steroid creams contain propylene glycol which explains why contact allergy to propylene glycol was high in our study. 5 patients (13.9%) showed positive reaction to these two agents in our study. Similar frequency 14% was reported for propylene glycol from North America[7] but sorbitan monoleate sensitization rate was very low (0.9%) in another study[132]

In our study, 4 patients (11%) showed positive reactions to chlorhexidine digluconate, bacitracin, propolis, eosin, phenyl mercuric acetate and imidazolidinyl urea.

Chlorhexidine which is commonly used antiseptic agent in India was positive in 11% of patients whereas in one meta analysis chlorhexidine positivity was 4%.[133]

Other studies showed sensitization rate to bacitracin, ranging from 6.7%,8%,24% whereas our study showed 11% positive patch test reaction.[7,130] Bacitracin and neomycin combinations are most commonly used ‘over the counter product’ in India leading to increased chance of contact allergy to bacitracin.

Our study showed high rate of contact allergy to propolis(11%) compared to a study from Canada(4%)[130]. This could be due to cross reaction of propolis with balsum of peru which is present in various cosmetics. Propolis is used for leg ulcer treatment in western countries but in India it is rarely used for this purpose.

Imidazolidinyl urea which is used as a preservative in corticosteroid creams was positive in 11.11% in this study, whereas in a study from North America imidazolidinyl urea positivity was 7%.[7]

Topical bacteriostatic preparation contains eosin mainly in the western countries. However in India it is not available. Phenyl mercuric acetate is used as a preservative in various steroid and antibacterial combination creams.

Amerchol L 101 and cetyl stearyl alcohol were positive in 3(8.3%) patients in our study whereas one study showed 7% Amerchol L 101 positivity. [130]Amerchol positivity in our study could be due to cross reaction with lanolin which is present in most of the emollients and tulle type of dressing.

In contrast to other studies (6%,2.3%),[130,134] our study sensitization rates to cetyl stearyl alcohol was high(8.3%). Cetyl stearyl alcohol is used as a preservative in almost all moisturisers and steroid creams.

In our study, only 2(5.5%) patients showed positive reaction to fusidic acid sodium, sorbic acid, triethanolamine, sorbitan sesquioleate, chloroacetamide and diazolindinyl urea .

Our study positivity rate to fusidic acid sodium salt was low (5.5%) compared with a study from Scotland (9%).[2] Fusidic acid sodium salt is not a frequent sensitizer.

Diazolindinyl urea which is used as a preservative in emollients, personal care products and sunscreen was positive in 5.5% in our study whereas in a western Study, diazolidinyl urea positivity was 4%[7]

Triethanolamine which is used as an excipient in various creams and ointments was positive in 5.5% in our study whereas in a study from Serbia, triethanolamine positivity was 2.7%[136]

Chloroacetamide is present in various cosmetics. Compared with Swiss study(1.5%) [119], chloroacetamide positivity(5.5%) is high in our study.

Rare allergens in our study were Nitrofurazone, 2,6 Ditert-butyl-4-cresol,chloramphenicol,benzoyl peroxide and budesonide which showed positive reactions in only one(2.8%) patient. None of the patient showed positive reaction to tixocortol-21-pivalate.

Although nitrofurazone is a known sensitizer in leg ulcer patient, in our study sensitization rate was low, because in India it is not a commonly used topical antibiotic.

Other studies showed prevalence of sensitization to budesonide, ranging from 2.3%[134], 2.9%[6], 3%[2] to 20%[135] but our study showed 2.8%. Tixocortol 21 pivalate and budesonide is most sensitive indicator of steroid allergy.

In our study only 2.8% of patients were positive for chloramphenicol. In India chloramphenicol is available mainly as eye drops and ointments. So rate of contact allergy was low in our study.

In our study benzoyl peroxide positivity was 2.8% whereas western literature it was 7%[130]. Unlike the western countries benzoyl peroxide is rarely used for leg ulcer treatment in India. So sensitization to bezoyl peroxide was low in ours.

In contrast to several studies (2%[135],2.3%[134]) in our study none of the patient showed positive patch test reaction to tixocortol 21 pivalate.

Various differences exist in the percentage of allergen positivity in our study as compared to western literature. In our study one patient had multiple (11) positive reaction which was considered as angry back syndrome.

Patients own products were patch tested in 5 patients ,One patient was patch tested with Fenlong ointment (Diclofenac+capsaicin), but patch test reading was negative.

Another patient was tested with mehaheal(colloidal silver) and centis cream (ayurvedic cream which contain Centella Asiatica extract: 1.5%).In that patient mehaheal patch test showed negative result but centis cream was positive. In our study, 3 patients were patch tested with T.Bact (Mupirocin) which showed negative results

CONCLUSION

CONCLUSION

Our study showed a high rate of contact sensitization in leg ulcer patients. Most common allergens in our study were 4-chloro 3-creso l(preservative in steroid creams),wood tar mix (cosmetic related to balsum of peru), framycetin sulphate (antimicrobial) followed by benzalkonium chloride (disinfectant) and thiomerosal (preservative ,antiseptic). Percentage of positive allergens reflects the local wound care practices for leg ulcer, particularly the use of topical steroids and antimicrobial. By avoiding that particular allergen we can prevent secondary sensitization which will promote the wound healing. So we recommend patch testing for leg ulcer patients with or without dermatitis, so as to prevent delayed wound healing.

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Picture 1 : Patient with leg ulcer

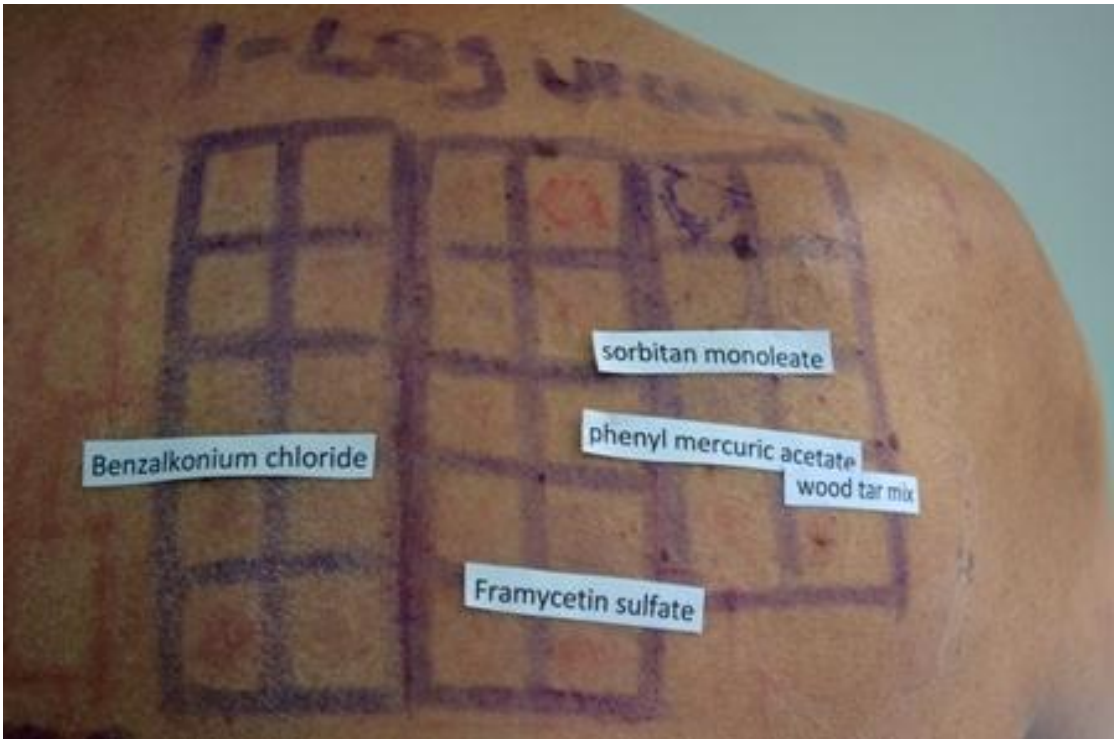
Picture 2: Leg ulcer with surrounding dermatitis

Picture 3 : Patch test kit – leg ulcer series antigens

Picture 4: Strips applied on patient's back

Picture 5: Leg ulcer with surrounding dermatitis

Picture 6: Same patient with wood tar mix positivity



Picture 7: Patient with multiple positivities

Picture 8: Grade 2+ positive patch test reactions

PATCH TESTING CONSENT FORM

I, the undersigned, do herby consent for undergoing PATCH TESTING.

I confirm that the details of the procedure, its side effects and benefits have been explained to me in a language that I understand. I have been given the opportunity to clarify any concerns that I have and sign this consent form freely and voluntarily.

I give my full consent for all of the aforementioned.

Name : _____

Signature : _____

ஒப்பதல் படிவம்

..... ஆகிய நான், பேட்சு பரிட்சை செய்து கொள்ள சம்மதிக்கிறேன். இந்த பரிட்சையைப் பற்றிய செயல்முறை மற்றும் பக்க விளைவுகள் அனைத்தும் எனக்கு நான் புரிந்து கொள்ளக்கூடிய மொழியில் மருத்துவர்களால் விளக்கப்பட்டது. இந்த பரிட்சையை செய்து கொள்ள நான் முழு சம்மதம் அளிக்கிறேன்.

கையொப்பம் :

பெயர் :

தேதி :

PATCH TEST – LEG ULCER PROFORMA

Date :

Personal Details

Name : Occupation : Hosp. No.

Age : Address & Phone No.:

Sex :

History

1. Duration of Ulcer:

0-3 month	3-6 month	6-1 year	1-5 year	>5 year

2. Varicose Vein : Yes / No

3. Pain : Claudication : Yes / No
   Rest Pain : Yes / No

4. Trauma : Yes / No

5. Anesthesia : Yes / No

6. Diabetes : Yes / No

7. Hypertension : Yes / No

8. Previous Treatment:

   Topical : Emollient :
   Antibiotics :
   Steroid :
   Antiseptic :
   Combination :
   Duration :

   Systemic : Antihistamine Antibiotic Steroid

   Surgery : Yes / No
   Details:

   Response to treatment : Improved / Not Improved / worked

9. Use of Stockings / Crepe Bandage: Yes / No

Examination

1. Varicose vein : Present / Not Present

2. Deformities of limb : Present / Not Present

3. **Ulcer :** size :

4. Site :

5. Bilateral / Unilateral :

6. Number :

7. Edges : Regular / Irregular

   Punched out / Sloping

8. Surrounding Skin

   Pigmentation : Present / Not Present

   Induration : Present / Not Present

   Dermatitis : Present / Not Present

9. Edema of the Leg :

10. Maggots :

11. Foul Smelling :

12. Peripheral Pulsation :

13. Diagnosis :

Investigations

1. CBC
2. S. Protein
3. RBS / FBS / PPBS / HbA1 C
4. Pus Culture / Sensitivity
5. Doppler — Arterial / Venous
6. Lupus Anticoagulant
7. Homocysteine
8. ANCA
9. AFB
10. X-ray
11. Biopsy

Results of ISS patch test : 48 hrs 72 hrs

LEG ULCER SERIES

S.No.	ANTIGEN	%	DAY	DAY		
				3	4	5
01	Control					
02	Amerchol L 101	50				
03	Fusidic acid sodium salt	2				
04	Chlorthexidine digluconate	0.5				
05	Benzalkonium chloride	0.1				
06	Nitrofurazone	1				
07	Bacitracin	5				
08	Cetyl Steary alchohol (Lanettee O)	20				
09	2,6 Ditert-buty1-4-cresol (BHT)	2				
10	Chloramphenicol	5				
11	Benzoylperoxide	1				
12	Propylene glycol	5				
13	Propolis	10				
14	Thimerosal (Merthiolate)	0.1				
15	Sorbic acid	2				
16	Eosin	5				
17	4-Chloro-3cresol (PCMC)	1				
18	Budesonide*	0.01				
19	Triethanolamine	2				
20	Framycetin sulfate	20				
21	Sorbitan Sesquioleate	20				
22	Tixocortol-21-pivalate	0.1				
23	Sorbitan Monoleate (Span 80)	5				
24	Pheny Mercuric acctate	0.01				
25	Chloroacetamide	0.2				
26	Diazolindinyl urea (Germall II)	2				
27	Imidazolidinyl urea (Germall 115)	2				
28	Wood tar mix (Pine, beech, Juniper, Birch)	12				
	COMPLETE SERIES					

*According to ESCD and EECDRG studies, test reading on recommended.

ABBREVIATIONS

DVT	Deep Vein Thrombosis
PG	Pyoderma Gangrenosum
ABPI	Ankle brachial pressure index
PDL	Pulsed dye laser
TRUE test	Thin layer rapid use epicutaneous test.
CVI	Chronic venous in sufficiency
ACD	Allergic Contact Dermatitis
BZK	Benzalkonium chloride
ROAT	Repeat Open Application test
BHT	Butylated hydroxyl toluene
PG	Propylene Glycol
TEA	Triethanolamine

MASTER CHART CODES

0	No, Negative
1	Yes, Positive
1-28	Leg ulcer series allergens